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PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY EMPHYSEMA*

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PULMONARY emphysema is one of the most common, disabling and chronically progressive diseases seen in a general hospital. The usual sequence of emphysema, bronchitis, fibrosis and progressive respiratory insufficiency has defied attempts at prevention or treatment.

General therapy of this disorder has included intermittent administration of oxygen and the use of bronchodilators and antibiotics — all of which increased the life span of these patients by minimizing the severity of acute bronchial infections.

Attempts at specific therapy have been varied. Costal chondrectomy was used by Freund[1] in 1906, with some improvement in the symptoms due to emphysema of long duration.[2] Compressed-air cabinets and intermittent abdominal compressors have been used to facilitate the difficult expiratory phase of respiration.[3] These were too cumbersome for general use. Abdominal belts, such as those described by Kountz and Alexander,[3] are of little value in patients with scaphoid abdomens, against which the belts can exert no real pressure.[4, 5]

Reich,[6] in 1924, was the first to study the effect of pneumoperitoneum on the ventilation of patients with emphysema. He observed elevation of the diaphragm by the injected air together with increased diaphragmatic excursion and consequent increased minute respiratory volume, reduction in dyspnea, greater ease in raising bronchopulmonary secretions and subjective improvement.

Unaware of Reich's previous work Piaggio-Blanco,[7] in 1937, reported clinical improvement in 2 patients with emphysema treated by large pneumoperitoneum injections of 1 to 5 liters of air. No subsequent reports of this treatment have appeared other than a general discussion of these authors by Banyai.[8]

TABLE 1. *Clinical and Pulmonary Ventilatory Data on 3 Patients with Advanced Fibroid Tuberculosis and Associated Emphysema, before and after Pneumoperitoneum Treatment.*

CASE NO.	SEX	AGE	TYPE OF TUBERCULOSIS	DURATION	PNEUMOPERITONEUM		MAXIMUM BREATHING CAPACITY	WALKING INDEX	VITAL CAPACITY
					DATE	AMOUNT			
		yr.					*liter/min.*	*%*	*cc.*
1	M	29	Bilateral apical fibrocavernous disease, with retraction and emphysema	7 yr.	10–47	None	40	(Unable to walk)	1260
					6–48	+	42	55	1350
					1–49	+++	49	53	2440
2	M	41	Far-advanced bilateral fibrocavernous disease, with emphysema	—	8–47*	++	56	41	1850
					10–47†	+	46	57	1600
3	M	48	Bilateral apical fibrocavernous disease, with retraction and emphysema	12 yr.	11–48	None	32	62	3080
					1–49	++	48	46	3140

*48 hr. after refill.
†6 wk. after refill.

SELECTION OF PATIENTS

The first 3 patients studied were receiving pneumoperitoneum treatment for active pulmonary tuberculosis. All had severe dyspnea when pneumoperitoneum was omitted and felt relieved when treatment was reinstituted. It was then observed that all 3 had marked pulmonary emphysema secondary to contracting fibrosis in areas of tuberculous disease. These findings were confirmed by physiologic studies (Table 1 and Fig. 1). This observation suggested to us the possibility of using pneumoperitoneum for the treatment of emphysema not associated with tuberculosis.

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Clinical criteria were then established for the acceptance for treatment of nontuberculous patients with emphysema. These required that each patient should have pulmonary insufficiency with dyspnea that was incapacitating for work, that cor pulmonale, if present, should be minimal, that pulmonary infection should have been adequately treated, that bronchoscopy and other studies should have ruled out tumor, active tuberculosis, bronchial obstruction and severe bronchiectasis, and that decompensated heart disease should not be present.

After this study had progressed sufficiently to demonstrate marked improvement in some patients, pneumoperitoneum treatment was extended to patients with severe emphysema, who were critically ill because of impaired tussive force and retained bronchopulmonary secretions after thoracic surgery. A total of 22 cases are here reported.

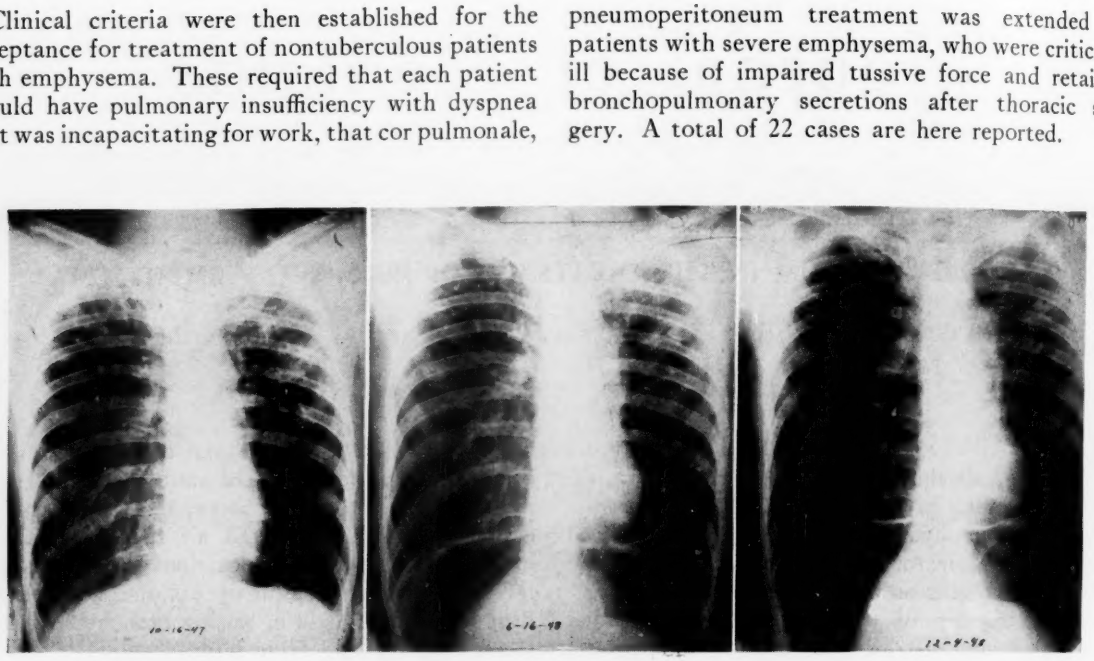

FIGURE 1. *Roentgenograms of the Chest in Case 1, Illustrating the Original Emphysema and the Degree of Pneumoperitoneum Associated with Improved Pulmonary Function.*
The roentgenogram on the left was taken on October 6, 1947, that in the center on June 16, 1948, and that on the right on December 4, 1948.

METHODS OF STUDY

All patients were admitted to the hospital for study prior to induction of pneumoperitoneum. In the history particular emphasis was placed on occupation, allergies and asthma, cardiorespiratory background and familial disease. The physical examination included observation of the character and quantity of the sputum and its investigation

TABLE 2. *Summary of Clinical Data from 16 Patients with Pulmonary Emphysema Treated by Pneumoperitoneum.*

Case No.	Sex	Age	Past History			Symptoms		
			Allergy	Cardiac	Other	Dyspnea	Cough	Sputum
		yr.						
4	M	61	0	0	0	+++	Severe	Copious
5	M	48	Asthma (to wool)	0	0	+++	Severe	Copious
6	M	56	0	0	0	++++	Severe	Copious
7	F	74	0	Arteriosclerotic heart disease; digitalis.	0	++++	Severe	Moderate
8	M	66	0	Arteriosclerotic heart disease; digitalis.	Paraplegia	++++	Severe	Copious
9	M	45	Asthma	0	Poliomyelitis	++++	Severe	Copious
10	M	52	Hay fever	Arteriosclerotic heart disease; digitalis.	Inguinal hernia	++++	Severe	Copious
11	M	56	0	0	Influenza	++++	Severe	Copious
12	M	65	0	0	Duodenal ulcer	++++	Moderate	Moderate
13	F	61	0	Hypertensive heart disease; digitalis.	Abdominal operations	+++	Moderate	Moderate
14	M	62	Asthma (20 yr.)	Digitalis	0	++	Moderate	Slight
15	M	58	0	0	0	++	Severe	Copious
16	M	66	0	Digitalis 0	0	+++	Moderate	Moderate
17	M	35	0	0	0	++++	Severe	Copious
18	M	59	0	0	0	++	Moderate	Moderate
19	M	44	Asthma (20 yr.)	0	0	++	Severe	Copious

*Arm to tongue, magnesium sulfate method.
†Not available.

for acid-fast organisms, estimation of the chest shape and measurement of the chest expansion. Special investigation of the cardiac status included determinations of the arterial and venous blood pressure and circulation time and an electrocardiogram. Bronchoscopy was performed in every case. Fluoroscopy of the chest was performed by the same observer before and after induction of pneumoperitoneum, with particular attention to diaphragmatic motion and "trapping" of air.

Pulmonary physiologic determinations were performed on all medical patients before and after induction of pneumoperitoneum but were omitted in the postoperative cases. These studies were intended to evaluate objectively changes in pulmonary function with treatment, eliminate patients suffering primarily from clinically undetected bronchial asthma or pulmonary fibrosis and establish criteria for the use of pneumoperitoneum in the treatment of emphysema. A detailed analysis of the physiologic studies has been reported elsewhere.[9]

Clinical Data

Table 2 summarizes the significant clinical data on 14 male and 2 female patients whose ages ranged from thirty-five to seventy-four years. All had far advanced pulmonary emphysema with chronic bronchial infection. The mentality seemed dulled in every case, apparently owing to chronic anoxia, and each patient was preoccupied with the very act of breathing. The patients were apprehensive and intolerant even of minor irritations.

were ambulatory but with severe restrictions. The last group could walk only slowly and could ascend one flight of stairs, but with distress. None had been able to work for several months prior to admission.

Cough and sputum were the next most distressing symptoms. Most patients complained of constant, severe, productive cough, and 10 patients produced 1 cupful or more of sputum per day. No history of hemoptysis was obtained.

Six patients had been treated with digitalis. In 3 of these, genuine heart disease was evident with at least one episode of cardiac failure; the remaining 3 were given digitalis empirically because of dyspnea. A slowly progressive loss of weight accompanying the increasing pulmonary symptoms was noted by all, but 2 patients were moderately well nourished.

No etiologic factors related to occupation could be found. Three patients gave a history of asthma, but in none was it severe. Two patients gave a family history of tuberculosis; the family history was noncontributory in the others.

One patient was paraplegic from an injury at birth; 1 had severe post-poliomyelitic scoliosis; 1 gave a history of duodenal ulcer with perforation nine years previously; 1 had undergone an appendectomy thirty-four years previously, with seven subsequent abdominal operations for adhesions; and 1 gave a history of severe influenza.

At the onset of pneumoperitoneum treatment all patients had normal temperatures and pulse rates, although most entered the hospital with signs of pulmonary infection. The resting respiratory

Table 2 (*Concluded*).

Case No.	Chest Shape	Blood Pressure	Venous Pressure	Circulation Time*	Electrocardiogram	Bronchoscopic Findings	Improvement		
							Subjective	Objective	Cough
4	Moderate barrel	165/95	60	25	Normal	Negative	++	+	++
5	Slight barrel	110/75	42	15	†	Negative	0	0	+
6	Barrel	160/100	†	†	Normal	Atrophic mucosa	0	0	0
7	Normal	175/100	75	14	"Myocardial damage"	Atrophic mucosa	++	++	++
8	Barrel	120/65	50	20	"Myocardial damage"	Lateral tracheal compression	++	+	++
9	Right scoliosis	100/75	116	14	Normal	Tracheal deviation to the right	+	++	+
10	Barrel	130/80	90	15	Left-axis deviation	Negative	0	+	+
11	Normal	124/80	90	16	†	Negative	++	++	++
12	Normal	168/110	160	13	Normal	Negative	++	++	+
13	Slight barrel	190/90	90	12	"Left ventricular enlargement"	Negative	++	+	+
14	Barrel	185/90	85	18	Normal	Negative	++	+	+
15	Normal	150/100	70	16	Normal	Negative	+	+	+
16	Slight barrel	120/80	55	17	Normal	Negative	++	++	++
17	Slight barrel	150/†	70	14	Right-axis deviation	Atrophic mucosa	0	0	++
18	Barrel	†	30	13	Left-axis deviation	Negative	0	0	+
19	Normal	120/80	110	10	Normal	Negative	0	0	+

Dyspnea was the most marked symptom in all cases. This was graded as ++++ for patients who were totally bedridden, +++ for those who were barely ambulatory, and ++ for those who

rates were elevated, and 5 patients were obviously cyanotic.

The shape of the thorax was barrel-like in 10 patients, and the spine was markedly scoliotic in

1. Rales, rhonchi and wheezes were present bilaterally in all patients. The chest expansion did not seem to correlate with the chest shape.

Blood-pressure determinations ranged from 110 systolic, 75 diastolic, to 168 systolic, 110 diastolic, and the venous pressures from 30 to 160. The circulation time, measured from the arm to the tongue by the magnesium sulfate method, varied from 12 to 20 seconds in all except 1 patient. In this case it was recorded at 25 seconds, but there was no other evidence of cardiac disease or obstruction to venous return.

The electrocardiogram was interpreted as normal in 6 patients. It showed right-axis deviation in 1, left-axis deviation in 2, intraventricular block in 2, "myocardial damage," as interpreted from ST-segment changes, in 2 and both left-axis deviation and intraventricular block in 1. Electrocardiograms were not obtained on 2 patients.

Laboratory examinations revealed hemoglobin values from 11.5 to 15 gm. per 100 cc., 1 patient showing 18 gm. on admission. Hematocrit values ranged from 38 to 50 per cent. The white-cell counts were within normal ranges. The urine examinations disclosed no significant abnormalities except in a patient who subsequently died of uremia.

Bronchoscopic examinations consistently demonstrated pale mucosa and loss of bronchial elasticity in the older patients. The younger patients sometimes failed to show even these changes. One patient had an unexplained bilateral compression of the trachea, with an hour-glass appearance in cross section. This was confirmed at autopsy, and no cause other than emphysema was found.

Postoperative Pneumoperitoneum

Three patients were given pneumoperitoneum after intrathoracic surgical procedures. The "stir-up regimen," tracheal catheter aspiration and bronchoscopy had been tried in all cases without adequate response. Pneumonectomy was performed for carcinoma in 1, esophagectomy for carcinoma in another, and lobectomy for chronic lung abscess in the third. All had complicating emphysema, with consequent postoperative dyspnea, cyanosis and ineffectual cough. One of these patients was approaching death because of retained bronchopulmonary secretions in spite of repeated bronchoscopy and tracheal aspiration. After pneumoperitoneum treatment he was able to raise secretions spontaneously and was so improved that pneumoperitoneum, begun a week after operation, was abandoned three weeks later. Treatment was continued after discharge from the hospital in the remaining 2 cases because freedom from dyspnea continued only with pneumoperitoneum (Table 3 and Fig. 2).

Table 3. *Summary of Clinical Data from 3 Surgical Patients Who Were Given Pneumoperitoneum for Relief of Symptoms Caused by Pulmonary Emphysema.*

Case No.	Sex	Age	Primary Disease	Operation	Respiratory Problem	Pneumoperitoneum Begun	Duration of Pneumoperitoneum	Result	Remarks
		yr.							
20	M	67	Carcinoma of esophagus	Left transthoracic esophagectomy and supra-aortic esophagogastrostomy	Emphysema and retained secretions	2 wk. postoperatively	6 wk.	Recovery	Patient died in 6 mo. of recurrent tumor
21	M	58	Chronic lung abscess, right upper lobe, of 4 mo. duration	Lobectomy	Emphysema and retained secretions	1 wk. postoperatively	1 mo.	Recovery	Patient well at 1½ yr.
22	M	65	Carcinoma of right lung	Right pneumonectomy	Emphysema and retained secretions	3 wk. postoperatively	5 mo.	Recovery	Patient well at 2 yr.

Pathology

The histopathology of pulmonary emphysema is well known.[3, 10] Two patients have died, 1 eight months and 1 four months after beginning pneumoperitoneum treatment. Post-mortem examination was performed in both. One of these patients gave a history of asthma of long duration and was little improved by pneumoperitoneum treatment, and autopsy confirmed our clinical impression of advanced pulmonary fibrosis, which was the principal cause of death. The other patient, who was paraplegic, was found to have classic pulmonary emphysema with bullae, blebs, ruptured alveolar sacs and narrowed bronchioles. Death was due to uremia.

Technic of Pneumoperitoneum

We have, in general, followed the method of pneumoperitoneum induction described by Banyai.[8] All patients were hospitalized and given moderate barbiturate and codeine sedation prior to the initial introduction of air. With the patient in semirecumbent position, a point lateral to the outer border of the rectus muscle and about 4 cm. below the costal margin in the left upper quadrant was se-

lected. After preparation of the skin and procaine infiltration, a small nick was made in the skin with a scalpel blade. The patient was instructed not to cough, and a No. 19 short bevel needle attached to tubing connected with the pneumothorax apparatus was introduced at an angle of 45° to the abdominal wall. The fascial layers were felt as they were penetrated, and, after two layers had been passed (external and internal oblique), the direction of the needle was changed to lie more nearly parallel with the anterior peritoneal surface. The needle was then pushed farther, and the transversalis fascia and peritoneum penetrated as one layer. The needle was held in this position while 50 cc. of air was injected and a manometric reading taken. If the pressure rose to more than +2 cm. of water and remained elevated, the needle was usually not in the free peritoneal space. It was then moved in or out until injection of air in small amounts did not elevate the pressure. The initial fill was continued to 700 to 1000 cc. and stopped either when the patient complained of a sense of fullness or when he was no longer able to refrain from coughing.

Two refills of 500 to 1000 cc. were then given at two-day intervals, and the patient was discharged to return for outpatient refills once every two weeks. No premedication was given for refills, but patients with a large volume of bronchopulmonary secretions were given postural drainage prior to refill to lessen the possibility of cough while the needle was in place.

After the pneumoperitoneum was well established, refills of 80 per cent helium and 20 per cent oxygen were used. We believed that an adequate level was more readily maintained during the two-week interval between refills by the use of helium.

Results

Of 22 patients treated, 13 spontaneously reported improvement, which was marked in 10 and moderate in 3 cases. One patient (Case 10) was objectively improved, but abdominal discomfort was moderately severe and precluded acknowledgment of the improvement. Subjective improvement was characterized by reduction in dyspnea, increase in exercise tolerance, ability to sleep flat in bed when previously unable to do so and ability to raise bronchopulmonary secretions more easily, with consequent reduction of cough (Table 2).

Induction of pneumoperitoneum was occasionally more difficult than in the usual patient with tuberculosis, but air was satisfactorily introduced in all cases. After the initial injection of air, most patients complained of an ache in the shoulder, and some complained of slight abdominal distress as well. In all but 2 cases discomfort disappeared within three days and usually within twenty-four hours. Loss of appetite was not noted; on the contrary, appetite increased with clinical improvement of the patients.

Some improvement in subjective symptoms frequently occurred immediately after the first or second injection of air. Obvious improvement continued during the first two weeks of treatment but maximal improvement was usually not present before six to eight weeks after induction. One patient was receiving almost constant nasal oxygen therapy, was unable to get out of bed and could not drink a glass of water at a normal rate. Three weeks after beginning treatment he was able to walk into the outpatient department and proudly demonstrate his ability to drink a glass of water at a normal rate.

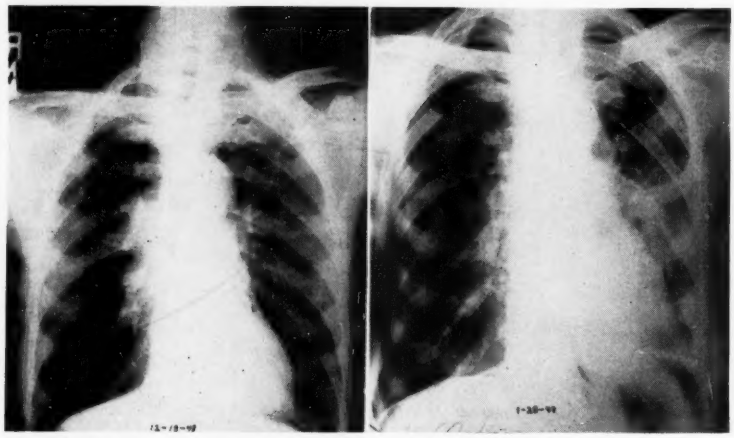

Figure 2. *Roentgenograms of the Chest in Case 20 before and after Esophagectomy and Supra-Aortic Esophagogastrostomy.*
The postoperative film on the right demonstrates the small degree of pneumoperitoneum necessary to increase tussive force.

One patient abandoned refills after two months because he was so improved that he thought the treatment was no longer needed. Re-examination four months after the beginning of treatment showed maintenance of the clinical improvement (Case 12).

Increased tussive force was one of the most impressive changes occurring with pneumoperitoneum treatment. All patients in whom retained bronchopulmonary secretions were a problem, stated that they could raise sputum more easily and needed to cough less frequently than before treatment. Rough measurements of force of cough confirmed this finding.

Fluoroscopy showed paradoxical movement of the diaphragm in 3 cases before treatment. The average range of diaphragmatic motion for all 13 patients was 10 per cent of normal. After treatment, no paradoxical motion was observed, and the average motion had increased to 40 per cent of normal (Fig. 3). No improvement was observed in the markedly impaired motion of the thoracic cage. Localized trapping of air, visualized in 1 case, was not altered by treatment. The pneumoperitoneums were small when compared to those maintained for the treatment of pulmonary tuberculosis.

Six patients believed that they were not markedly improved. However, all acknowledged that their cough was more effective during treatment (Cases 5, 6, 10, 17, 18 and 19). None were made worse by pneumoperitoneum.

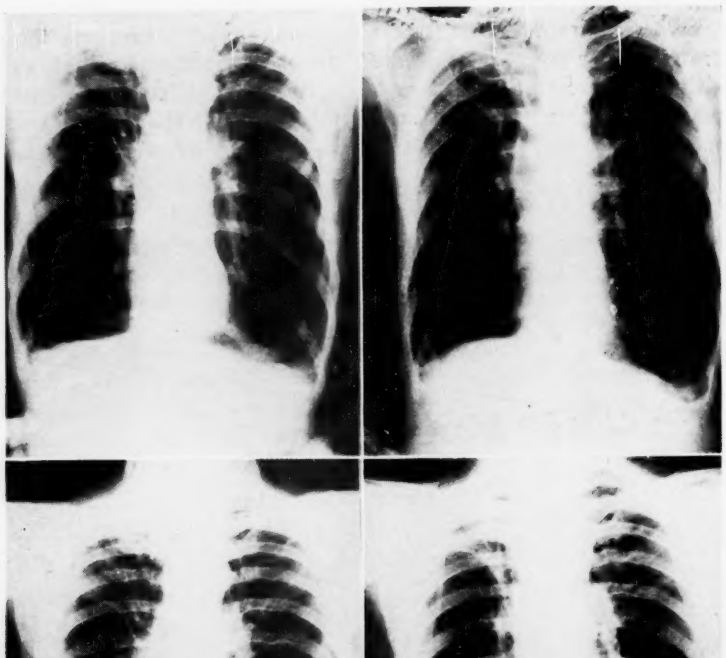

FIGURE 3. *Inspiratory and Expiratory Chest Roentgenograms of a Patient with Advanced Pulmonary Emphysema, before and after Pneumoperitoneum Treatment. The inspiratory position is on the left. Note that prior to pneumoperitoneum treatment the diaphragm is lower in expiration than in inspiration.*

RESULTS OF PHYSIOLOGIC STUDIES

The method of physiologic study was generally followed as outlined by Baldwin et al.[11, 12] and is described in detail elsewhere.[9] The total lung capacity was nearly normal in all patients although marked changes were evident in the components of this total lung volume: the residual air was more than doubled at the expense of the vital capacity, which was reduced to an average of 60 per cent of

normal. Pneumoperitoneum corrected this shift markedly by increasing the average vital capacity from 1989 to 2345 cc. and decreasing the average residual air from 2677 to 1980 cc. The combined

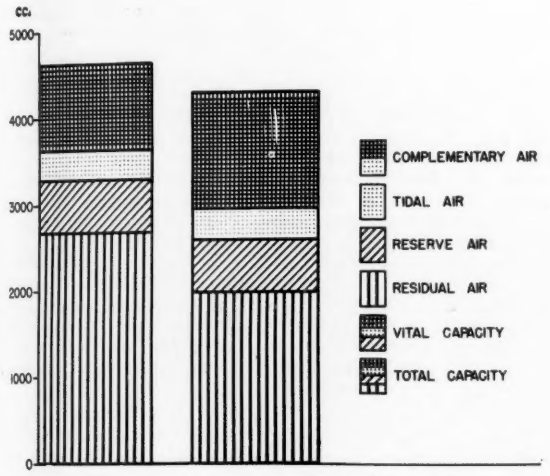

FIGURE 4. *Mean Total Lung Volumes of 11 Patients with Emphysema before and after Treatment with Pneumoperitoneum.*

effect was a slight reduction of the total capacity (Fig. 4). When the vital capacity was separated into reserve air, tidal air and complementary air,

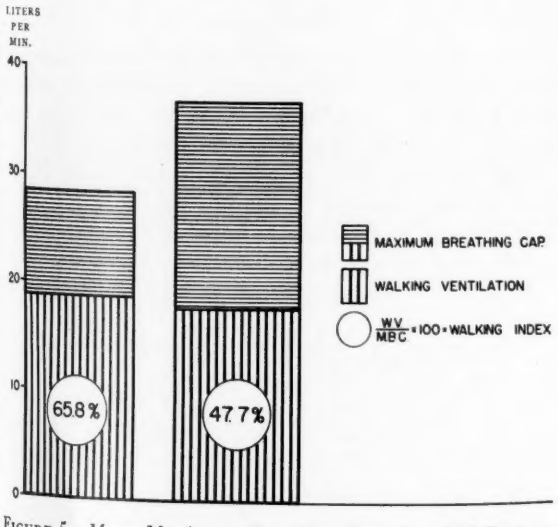

FIGURE 5. *Mean Maximum Breathing Capacity of 13 Patients with Emphysema before and after Treatment with Pneumoperitoneum.*

it became evident that the only component altered by pneumoperitoneum treatment was the complementary air. This was increased from a mean of 1388 to 1728 cc.

The maximum breathing capacity was much more severely impaired than the vital capacity and improved from a mean of 29 liters per minute before treatment to 37 liters per minute after treatment. The walking ventilation was chosen as a mild form of exercise test.[13] This was not elevated before treatment and decreased only 1 liter per minute after treatment. The dramatic reduction in walking dyspnea index[11] from 66 to 48 per cent was chiefly due to an improved maximum breathing capacity (Fig. 5). This improvement in maximum breathing capacity following pneumoperitoneum treatment of patients with emphysema is in contrast to a decreased maximum breathing capacity obtained in patients without emphysema.[14]

No change was observed in the minute oxygen consumption after treatment, whereas the minute

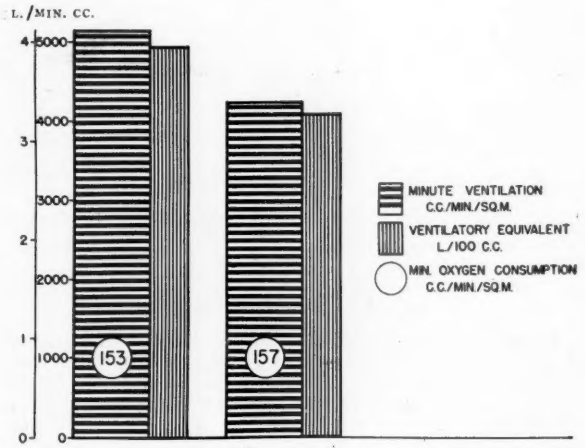

FIGURE 6. *Mean Minute Ventilation, Ventilatory Equivalent and Minute Oxygen Consumption in 12 Patients before and after Pneumoperitoneum Treatment.*

ventilation was reduced in all cases. This relation, which is defined as the number of liters breathed per 100 cc. of oxygen absorbed, was expressed by a fall in ventilatory equivalent from a mean of 3.28 to one of 2.72 liters. In other words, 560 cc. less air had to be breathed after treatment to absorb the same amount of oxygen as before treatment (Fig. 6).

Inhalation of a bronchodilator aerosol before pneumoperitoneum treatment showed an increase in maximum breathing capacity of over 10 per cent in only 2 cases.[15] Several of the patients who demonstrated a small maximum breathing-capacity increase with aerosol before pneumoperitoneum treat-

ment showed a greater increase after pneumoperitoneum treatment. This suggested that bronchospasm, previously masked by the effects of emphysema, became more evident as the emphysema decreased. Vital-capacity determinations showed only small and unrelatable changes before and after treatment (Fig. 7).

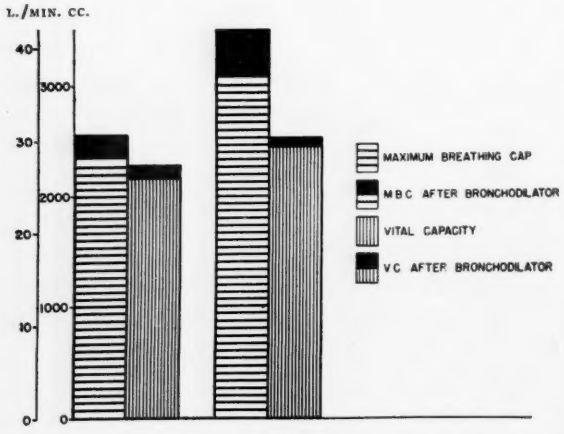

FIGURE 7. *Mean Change in Maximum Breathing Capacity and Vital Capacity following Administration of Bronchodilator Aerosol before and after Pneumoperitoneum Treatment of 9 Patients.*

CASE REPORTS

CASE 1. E. Z. (B.C.H. Sanatorium 19648), a 29-year-old single man with a 7-year history of tuberculosis, had refused adequate treatment. On his last admission he had far-advanced bilateral fibrocavernous disease. This responded to streptomycin therapy so that fibrosis of the upper lobes developed, with elevation of the pulmonary hili and marked "compensatory" emphysema of both lower lobes. However, he remained a "respiratory cripple" and required almost constant nasal oxygen at rest in bed. Pneumoperitoneum produced marked subjective improvement in the respiratory symptoms, and oxygen therapy could be discontinued. This improvement was confirmed by ventilatory studies. Now, in spite of a negative sputum, the patient cannot leave the sanatorium because weekly refills are necessary to balance the pneumoperitoneum at + to +++; either less or more air results in recurrent respiratory distress (Fig. 1).

CASE 11. F. S. (M.M.H. 335416), a 56-year-old man, gave a history of chronic cough for 10 years prior to admission with gradually increasing exertional dyspnea. He raised 2 or 3 cupfuls of mucopurulent sputum daily, and for the year prior to admission he had been unable to work. There had been a 40-pound weight loss in 3 years. The temperature was 100°F., the pulse 100, and the respirations 28 per minute. Bronchoscopy and determinations of blood pressure, venous pressure and circulation time were all within normal range. Roentgenograms of the chest suggested marked bilateral emphysema with diffuse fibrosis. He was treated with antibiotics, postural drainage and bed rest, with little improvement other than a fall of the temperature to normal. After preliminary studies, pneumoperitoneum was induced. The patient reported a gradual improvement in exercise tolerance and lessening of bronchial secretions, and for the first time in 5 years he was able to sleep flat in bed. Pneumoperitoneum refills were continued in the outpatient department; the clinical improvement persisted and was confirmed by repeated studies of pulmonary function.

CASE 17. F. C. (B.C.H. 1304872), a 34-year-old man, gave a history of chronic cough for 10 years productive of large quantities of thick, yellow sputum. For the 6 months preceding admission exertional dyspnea had so increased that he finally entered the hospital unable to walk. Physical examination showed a thin, dyspneic and cyanotic man with a normal temperature but respirations of 30 and a pulse rate of 120 beats per minute. Roentgenograms of the chest revealed bilateral irregular mottling, a long, thin chest and a low diaphragm. The diaphragm moved well, however, as noted on fluoroscopy. Treatment with penicillin, bed rest, postural drainage and nasal oxygen brought moderate improvement. It was thought that pneumoperitoneum might offer further improvement, but studies of pulmonary function showed a relatively good maximum breathing capacity of 75 liters per minute. The arterial oxyhemoglobin saturation was found to be 71 per cent at rest and 85 per cent at rest with nasal oxygen. These findings confirmed the impression of predominant pulmonary fibrosis, but pneumoperitoneum was tried. This was of no benefit and was discontinued after 1 month. Six months after admission the patient was discharged home but required oxygen intermittently throughout the day and was still totally disabled.

CASE 21. G. L. (B.C.H. 1306671), a 58-year-old man, entered the hospital with pneumonia of the right upper lobe from which mixed anerobic and aerobic bacteria were cultured. After 5 months of intensive medical treatment the acute infection had apparently healed, but a chronic lung abscess persisted. Moderately severe pulmonary emphysema was also present. Lobectomy was therefore performed. The postoperative course was complicated by retained endobronchial secretions. Tracheal catheter aspiration and bronchoscopy were used, but the severe emphysema persisted and constant nasal oxygen was necessary. One week after the operation, a pneumoperitoneum was induced. This increased the tussive force immediately, and the patient improved rapidly. He was discharged on the 14th postoperative day; pneumoperitoneum was continued for 2 more weeks and then abandoned. The patient was well 1½ years later.

DISCUSSION

The most striking effect of pneumoperitoneum was the marked improvement in tussive force, which was apparent even in patients not otherwise improved and in those with severe pulmonary fibrosis. It also appeared to be the most important factor in the improvement of the postoperative patients. The airway was cleared, the constant stimulus to cough was diminished, bronchial secretions were lessened, and the general state of the patient improved.

The mode of action of pneumoperitoneum to produce such a dramatic improvement could be seen at fluoroscopy. The flattened diaphragm of a patient with advanced emphysema was incapable of further contraction. When the normal diaphragmatic arch was restored, contraction downward again became possible. Moreover, air, a gaseous medium, may be compressed by the strong muscles of inspiration so that some additional pneumatic impetus may be given the diaphragmatic recoil on expiration. Our own studies, which confirmed this finding reported by others, are illustrated in Figure 1.

The diaphragm was elevated by the air because it was the only movable segment of the peritoneal

cavity after the rectus muscles were tensed. Persons with thin and relaxed abdominal walls therefore require more air to effect diaphragmatic elevation than those with tense abdominal walls. Belts and binders are of little value for thin persons because there is nothing to compress, but, after air has been given, a binder may cause even further improvement.

The demonstrated reduction in the volume of functional residual air implies increased efficiency of gaseous diffusion in the lungs. Improvement of alveolar gas mixing is perhaps the single most significant physiologic change brought about by pneumoperitoneum in patients with emphysema. This illustrates also that one cannot completely separate the mechanical or ventilatory aspect of pulmonary function from the gas exchange or alveolorespiratory aspect; improvement of one here implies improvement of the other.

It must be emphasized that patients in this series were in effect pulmonary derelicts who were chronically anoxic, and some of them actually were in a preterminal state. Their pulmonary function was reduced to such an extent that even with 100 per cent improvement of maximum breathing capacity they remained in borderline pulmonary decompensation. This was clinically apparent in some of our patients, who, after expressing pleasant surprise with the initial improvement following treatment, soon began to complain again, apparently forgetting how much worse their symptoms had formerly been. Pneumoperitoneum can only be expected to improve the mechanical efficiency of functioning pulmonary tissue; it cannot be expected to restore function to permanently damaged portions of the lung.

These clinical observations and their objective laboratory confirmation demonstrated that pneumoperitoneum is of value in the treatment of patients with far-advanced pulmonary emphysema. Improvement may be expected if patients are selected for treatment who have far-advanced pulmonary emphysema without significant pulmonary infection. However, patients with emphysema associated with active pulmonary tuberculosis or the usual chronic bronchial infection also improved because of the increased ability to clear the bronchial tree of secretions. Patients with pulmonary emphysema associated with bullae and giant cysts were not improved by this treatment (Case 6). Advanced pulmonary fibrosis may also be a cause of failure, as in 3 cases in this series (Cases 5, 17 and 18 in Table 2 and Fig. 8). Patients with emphysema in whom thoracic surgery is obligatory may occasionally be nursed through the postoperative period and a fatal outcome avoided by well timed induction of pneumoperitoneum.

We believe that the indications and limitations of pneumoperitoneum in the treatment of far-advanced pulmonary emphysema are clear. The place of pneumoperitoneum in the treatment of early and moderately advanced emphysema is not yet defined. However, one may conjecture that the unfortunate cycle of emphysema, infection and fibrosis might be slowed in some cases by the earlier institution of this treatment.

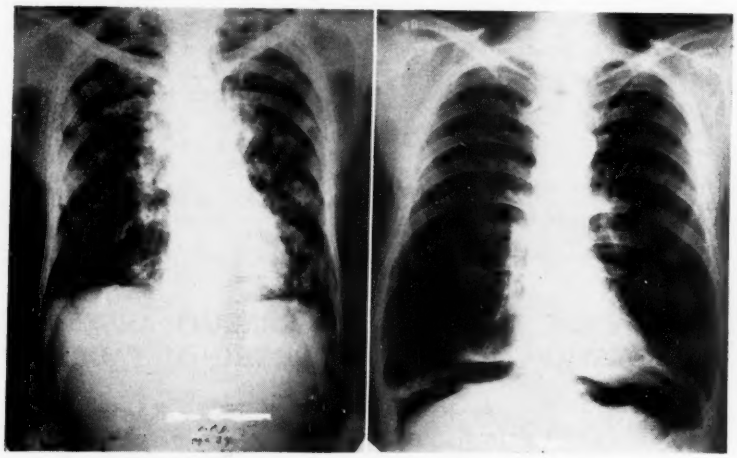

FIGURE 8. *Roentgenograms of 2 Patients with Pulmonary Emphysema Who Were not Improved by Pneumoperitoneum Treatment.*
Note the extensive fibrosis evident in the film on the left and the large right basilar bleb shown in the film on the right.

Summary

Twenty-two patients with pulmonary emphysema were treated with pneumoperitoneum. In 3 of these, the emphysema was "compensatory," secondary to contracting fibrosis in areas of tuberculous disease. Symptoms of respiratory inadequacy were lessened in all patients in this group.

Sixteen patients with far-advanced "obstructive" emphysema were studied by clinical and physiologic methods before and after treatment with pneumoperitoneum. Ten of these were subjectively and objectively improved.

Three patients were given pneumoperitoneum after thoracic surgery because of severe symptoms due to associated pulmonary emphysema. Improvement was noted in all 3.

The technic, indications and contraindications of pneumoperitoneum treatment of pulmonary emphysema are discussed.

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AN ADVERSE EFFECT OF BAL IN A CASE OF SUBACUTE ARSENICAL POLYNEURITIS, WITH OBSERVATIONS ON PORPHYRIN METABOLISM*

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BRITISH anti-lewisite (BAL) was first developed by Peters and his co-workers[1] for the treatment of arsenical war-gas poisoning. It soon became apparent, however, that this compound could be used in the treatment of arsenical poisoning in general.

Clinically, BAL has been used most extensively in the therapy of arsenical dermatitis, but it has also been employed in the treatment of blood dyscrasias due to arsenic, post-arsenical jaundice, arsenical encephalopathy and various other manifestations of arsenical poisoning. With the exception of post-arsenical jaundice, good results have been reported with this drug.

It is the purpose of this paper to present a case of arsenical neuritis due to arsenic trioxide treated with BAL. This case is of particular interest since BAL caused a definite and dramatic aggravation of neurologic signs and symptoms. In an intensive search of the literature, no similar report was found.

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Case Report

D. N. G., a 54-year-old rural mail carrier, was admitted to St. Barnabas Hospital on December 10, 1948, with complaints of ataxia and numbness of the arms and legs. The patient stated that he was in his usual state of health until 13 days prior to admission, when he noted the onset of vomiting and diarrhea. For 3 consecutive days prior to the onset of his illness he had taken several drinks from a bottle of whisky later proved to be contaminated with arsenic trioxide. On the day the illness began, the vomiting was mild, and he had two or three loose stools. There was no hematemesis or melena. The next day he had one black stool. Two days later he noted weakness of the hands and difficulty in handling the mail sacks. After a few more drinks from the same whisky bottle, the diarrhea for the first time became very severe, but there was no further melena.

Eight days prior to admission, the patient noted yellow vision. On the next day weakness, ataxia of the legs and right arm and numbness of the right hand and arm appeared. During the next three days the weakness progressed, and the numbness spread to involve the other arm and both legs below the knee. Rather severe muscle pain also began at this time.

History by systems revealed slight stiffness of the neck. There was no swelling of the eyelids. The complete absence of any genitourinary complaints is worthy of note.

Physical examination revealed a well developed, well nourished man, who did not appear to be acutely or chronically ill. Examination of the head, neck, chest, heart and abdomen was negative. There was a blotchy, erythematous rash over the anterior portion of the chest that disappeared within 48 hours.

The temperature, pulse rate, respiration, and blood pressure were within normal limits.

Neurologic examination showed the cranial nerves to be intact. Bilateral triceps-muscle and grip weakness and mild weakness of all the muscle groups of the lower extremities

was present. There was a hyperalgesia of the palmar surfaces of the hands, and the dorsum of the toes, but subjectively there was numbness of the glove-stocking type. Vibration sense was absent in all four extremities. Position sense was decreased in the left leg. There was definite muscle tenderness. Deep tendon reflexes were equal and brisk in both upper extremities, but were markedly reduced in both legs. There was a positive Gordon sign on the right, but all other toe signs were negative. Abdominal and cremasteric reflexes were present. Finger-to-nose, finger-to-finger, and heel-to-knee tests were slightly impaired. The Romberg test was positive. The patient walked with a wide base, with some ataxia and a tendency to fall forward.

Examination of the blood disclosed a hemoglobin of 12.1 gm. per 100 cc. on admission, gradually increasing to 15.2 gm. in a period of 1 month. Red-cell and white-cell counts were normal. Differential counts revealed a relative lymphocytosis (42 to 45 per cent), with the polymorphonuclear leukocytes ranging from 32 to 42 per cent. A striking feature of the differential count was a persistence of eosinophilia, the count varying from 13 to 20 per cent for the 1st week of hospitalization. After this time, the blood picture returned to normal. No basophilic stippling was seen. The blood serologic findings were negative. The blood urea nitrogen was 12 mg. per 100 cc. Urinalysis revealed a faint trace of albumin, with occasional red and white cells in the sediment. The urinary output ranged from 900 to 1700 cc. per day.

Two spinal fluids were obtained at a 17-day interval. The fluid was clear with a pressure equivalent to 200 mm. of water. One cell was found on each occasion, and the spinal-fluid protein was 83 and 120 mg. per 100 cc. respectively. The colloidal-gold curve, serologic and bacteriologic findings, sugar and chloride were all normal.

Liver-function tests showed the serum bilirubin, thymol turbidity, cephalin flocculation and urine urobilinogen to be within normal limits. Phenolsulfonphthalein excretion was 60 per cent in 1 hour. A concentration test demonstrated a maximum specific gravity of 1.016. The stools were negative for ova, parasites and blood on several occasions. Muscle biopsy was negative for trichinosis and periarteritis nodosa.

The patient was treated conservatively for a period of 2½ weeks, with essentially no change in the clinical or neurologic picture. On December 29 the urine was examined for heavy metals, and 1.12 mg. of arsenic trioxide was found in a 24-hour specimen. Other studies revealed the hair to contain 2.3 mg. of arsenic trioxide per 100 gm. The whisky referred to above contained 150 mg. per 100 cc.

In spite of the time that had elapsed since the ingestion of the arsenic, it was decided to give the patient the benefit of a therapeutic trial with BAL. This was started on January 12, 1949. He was given BAL in a dosage of 2.5 mg. per kilogram of body weight or 166 mg. per day, divided into equal doses every 4 hours for the first 2 days, and twice a day subsequently.

Four days after BAL therapy was initiated, the patient exhibited biceps and triceps hyporeflexia for the first time, and definite areas of anesthesia of the hands and feet were noted. Position sense was lost in the lower extremities. On the next day he was found to be suddenly and strikingly worse. He had complete anesthesia extending up to above the umbilicus and such severe inco-ordination of the upper extremities that he was unable to smoke or feed himself. The reflexes in the legs disappeared. In view of the abrupt onset and rapid progression of neurologic involvement coincident with BAL therapy, it was considered unsafe to continue this medication, and the drug was stopped on January 15.

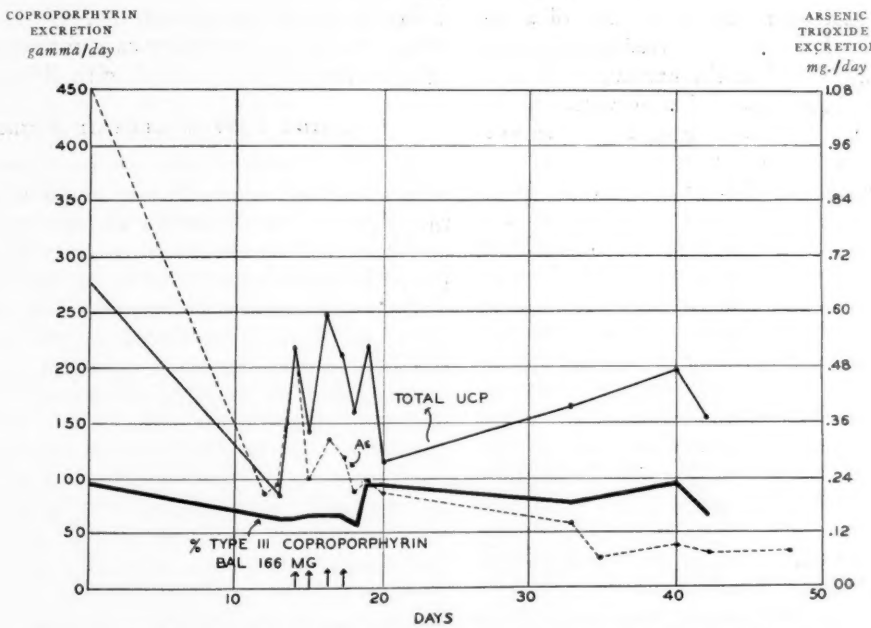

FIGURE 1. *Urinary Coproporphyrin and Arsenic Excretion in Relation to BAL Therapy.*

Subsequently, the patient slowly improved, and on discharge to a Veterans Administration Hospital on March 17 deep and superficial sensation in the lower extremities had partially returned. Power and co-ordination remained markedly impaired, and atrophy of the muscles of the hands, thighs and calves was present. The reflexes remained unchanged. Transient minor psychotic behavior was noted on February 3.

In addition to BAL therapy, the patient received physiotherapy, and a high-carbohydrate, high-protein diet with adequate vitamin supplements, both orally and intramuscularly.

Serial urinary arsenic and coproporphyrin studies were carried out* (Fig. 1). The erythrocyte protoporphyrin was 240 gamma per 100 cc. of red cells on December 30, 1948, a moderately elevated value.

DISCUSSION

This case presented a difficult diagnostic problem. The peripheral neuritis, albuminocytologic dissociation and normal temperature fit the picture of a Guillain–Barré syndrome, and this was the initial diagnosis.[2] The pronounced eosinophilia

*We are indebted to Miss Violet Hawkinson for measuring the urinary coproporphyrin.

with nervous-system involvement remotely suggested trichinosis, but muscle biopsy failed to confirm this.

The mild onset of the illness, with the very rapid development of peripheral neuritis, absence of kidney and liver involvement and presence of eosinophilia, was atypical for arsenic poisoning.[3-8] However, when inorganic arsenic was found in the whisky, urine and hair, the diagnosis of arsenic poisoning was established.

The most unusual feature of this case was the adverse response to BAL therapy. The Council on Pharmacy and Chemistry of the American Medical Association[9] had no record in its files of a response to BAL similar to that reported in this case, nor was such a case found in the literature. It was believed that the long period of observation prior to therapy, with no neurologic progression, served as an adequate baseline, and that the rapid neurologic changes following BAL therapy were more than coincidental. Serial urine arsenic and coproporphyrin determinations during BAL therapy showed a suggestive increase in excretion of these compounds, although the findings were not conclusive. Further arsenic ingestion to account for the acute exacerbation of neurologic symptoms could not be excluded with certainty. However, the fact that only a hospital diet was taken, the very close time relation between the increase in symptoms and BAL administration and the urinary findings tended to incriminate the BAL therapy in this respect.

BAL in this case was given in the usual dosage as outlined by the Council on Pharmacy and Chemistry of the American Medical Association.[10] Furthermore, the BAL used was investigated for sterility and chemical changes, and was found to be normal in every respect.[11] When given in toxic doses, BAL has been known to produce nausea, vomiting, headaches, burning of the mouth, throat and eyes, generalized muscular aches with tingling of the extremities and a sense of constriction in the chest.[10] No severe neurologic involvement of the type seen in this case has been reported as a toxic effect of this drug in human beings.

Koppanyi and Sperling[12] have reported intense stimulation of the central and parasympathetic nervous system following BAL and sodium arsenite administration in rabbits. They postulate that this reaction may be due to the formation in the body of a new substance possessing these stimulating effects. It is possible that the adverse response to BAL in the case reported above was likewise due to the formation of an arsenic BAL complex, which was injurious to the central nervous system. Randall and Seeler[13] emphasize the fact that BAL should not be used indiscriminately in the treatment of metal poisoning, because studies on animals indicate that it actually enhances the toxicity of certain metals.

Eagle and Magnuson[14] found that the mortality of arsenic poisoning increased proportionately to the delay in treatment with BAL. It is generally agreed that BAL should be administered early in the course of the disease in order to be effective. Welfare[15] described a case of arsenical dermatitis during Mapharsen therapy, in which treatment was instituted three weeks after the onset of symptoms, with a good response. However, Garner,[16] who treated a case of arsenical polyneuritis six weeks after the onset of symptoms, noted no change in the clinical course or excretion of arsenic in the urine, and stated that when arsenic is fixed to tissues it cannot be displaced through administration of BAL. This is the only other case of arsenical neuritis that we have found treated with BAL.

Urine Coproporphyrin Studies

In their review of the urinary coproporphyrins in health and disease Watson and Larson[17] discuss the effects of heavy metals on the coproporphyrin excretion. They state that coproporphyrinuria (Type III) has come to be recognized as a regular feature of lead intoxication, but add that data on the effect of other metals on the urinary coproporphyrin excretion is much more fragmentary. Increases following mercury administration have been observed. Hoerburger and Fink[18] isolated coproporphyrin III from the urine of a patient receiving arsphenamine. Brunsting, Brugsch and O'Leary[19] and Scolari[20] found increased coproporphyrin excretion in patients receiving arsphenamine. Watson and Larson[17] described a case of chronic poisoning characterized by hyperkeratosis, peripheral neuritis, anemia and excess arsenic in the urine and the hair. The urine coproporphyrin excretion ranged from 1 to 3.2 mg. per twenty-four hours, and the erythrocyte protoporphyrin was 200 to 240 gamma per 100 cc. of erythrocytes (usual normal range, 10 to 40 gamma). This patient, however, had been exposed to lead, and basophilic stippling was noted in the peripheral smear, suggesting the presence of lead intoxication as well as arsenic poisoning. Data concerning the erythrocyte protoporphyrin level in arsenic poisoning are apparently not available. In the case presented above, the erythrocyte protoporphyrin was distinctly elevated.

Schwartz and Zagaria[21] reported that the injection of arsenic into animals resulted in considerable increase of urinary coproporphyrin III, of short duration.

The literature is thus relatively sparse regarding coproporphyrin excretion in arsenic poisoning, and for this reason the present case is thought to be of unusual interest. It should be noted that high urinary coproporphyrin values (predominately Type III isomer) were present in this case (Fig. 1), and its excretion roughly paralleled the urinary arsenic excretion. It is also important that the findings suggest that BAL temporarily caused a slight in-

crease in the urinary excretion of arsenic and coproporphyrin. Luetscher, Eagle and Longcope[22] found a definite increase in urinary arsenic excretion in 16 patients with arsenical intoxication treated with BAL. On no occasion was there a decreased excretion during BAL therapy. It is possible that arsenic excretion was not further increased in this case because of the late administration of BAL in relation to the stage of the intoxication.

Summary

A case of arsenical polyneuritis treated with BAL is presented. Marked aggravation of neurologic symptoms and signs followed the administration of BAL in the usual dosage. This is believed to be the first report of such an adverse response to BAL during treatment of arsenical poisoning. Possible explanations for this response are considered.

Serial urinary arsenic and coproporphyrin studies are described. The urinary Type III coproporphyrin excretion was markedly elevated, and the erythrocyte protoporphyrin considerably elevated. BAL therapy caused a slight increase in the urinary excretion of arsenic and coproporphyrin, although the findings were not conclusive.

We are indebted to Dr. C. J. Watson for his advice and suggestions in the preparation of this report.

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CERVICAL OSTEOMYELITIS AND URINARY-TRACT INFECTION CAUSED BY *ESCHERICHIA COLI**

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CERVICAL osteomyelitis secondary to urinary-tract infection with *Escherichia coli* is rare. Kusunoki[1] was able to find reports of only 6 cases of osteomyelitis as a complication of urinary-tract infection. Three patients had metastatic abscesses in the vertebral column — 2 in the lumbar area, and 1 in the dorsal region. The other 3 had involvement of the humerus, femur and tibia. The causative organism was probably *Staphylococcus aureus* in 2 cases, staphylococcus (unspecified type) in 1 and *Proteus vulgaris* in 1, and in the other 2 cases the organism was not mentioned. The case reported by Kusunoki was a pyocyaneus osteomyelitis in conjunction with a pyelonephritis caused by the same organism.

In 1940 Schein[2] reported the isolation of *Pseudomonas aeruginosa* from the osteomyelitic cavity and urinary tract of a patient. Richardson and Ranking[3] described the autopsy findings in a patient who died of septicemia caused by *Esch. coli* secondary to osteomyelitis of both tibias and the right fibula. A large amount of pus containing *Esch. coli* was found in the subarachnoid space. Leukocytes and *Esch. coli* were found in the urine on one occasion during the course of the disease. The author stated that, "There was a diverticulosis of the descending colon, which presumably was the source from which the organisms reached the blood stream, bones and meninges."

Deming and Zaff,[4] in 1942, reported 3 cases of vertebral osteomyelitis secondary to urinary-tract infection following prostatic surgery. They were of the opinion that the spread of the infection took place via the route described by Batson — that is, a direct venous pathway from the prostatic and periprostatic veins to the vertebral veins. Organisms were obtained from the site of the osteomyelitis in only 1 case and were reported as a large gram-positive bacillus and a *Staph. aureus*. It was their recommendation that all patients with spinal osteomyelitis "have a more thorough urinary tract study for infection, because this portal is the most logical of all indirect ways of transmitting an infection which involves the bodies of the vertebrae."

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements made and conclusions drawn by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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The following case is unusual because pure cultures of *Esch. coli* were found in the urinary tract as well as in osteomyelitic cervical vertebras.

CASE REPORT

A 55-year-old Italian man was admitted to the hospital on January 26, 1949, with the chief complaint of severe pain in the neck of 5 weeks' duration. Eighteen months prior to admission he had entered another hospital because of frequency of urination and the passage of cloudy urine. A culture of the urine revealed *Esch. coli*, and a diagnosis of pyelonephritis was made. An intravenous pyelogram at that time showed poor concentration of the dye in both kidneys. He continued to have urinary symptoms until the present admission. Four weeks prior to admission he had re-entered the other hospital because of severe pain in the back of the neck radiating to both shoulders. At that time there was marked tenderness and spasm of the muscles of the neck. Culture of the urine showed an extensive growth of *Esch. coli* on several occasions. The patient was given penicillin, and the temperature, which had risen to 103°F. on the 2nd hospital day, gradually returned to normal during the 1st week. Because of the persistent bacilluria he was given 2 gm. of streptomycin daily for 2 weeks. X-ray findings of severe destruction of the third, fourth, fifth and sixth cervical vertebras led to transfer to the Veterans Administration Hospital.

Physical examination showed a patient in acute pain, which was aggravated by motion. He resisted any movement of the head and neck, and there was pain on palpating the cervical spine and shoulders. The maximum point of tenderness was over the sixth and seventh cervical dermatomes. Arm motion was free but caused pain in the cervical region. X-ray films (Fig. 1) revealed extensive destruction of the anterior bodies of the third, fourth, fifth and sixth cervical vertebras, with destruction of the intervertebral disks between the third and fourth and between the fifth and sixth cervical vertebras. There were nongranular sequestrums anteriorly and a tremendous increase in the retropharyngeal and retroesophageal spaces. Lipiodol studies of the upper esophagus revealed the presence of a posterior pharyngeal tumefaction, which appeared to be secondary to an acute osteomyelitis with abscess formation displacing the esophagus anteriorly.

Examination of the blood disclosed a hemoglobin of 12.5 gm. per 100 cc. and a white-cell count of 13,200, with 73 per cent neutrophils, 18 per cent lymphocytes, 4 per cent monocytes and 5 per cent eosinophils. Culture of the urine on admission revealed *Esch. coli* and *Alcaligenes faecalis*. Subsequent cultures revealed only *Esch. coli*. Three blood cultures remained sterile.

Shortly after admission the patient began to experience dysphagia. On the 3rd hospital day, Crutchfield head-traction tongs were applied under local anesthesia, and a 7.6-cm. oblique incision was made parallel to the anterior border of the left sternomastoid muscle. The muscle and carotid sheath were reflected laterally, and the omohyoid was reflected downward and medially. A plane was developed between the esophagus and the prevertebral fascia. The fascia was found to be bulging, and exploration revealed approximately 10 cc. of serosanguineous fluid and a moderate amount of necrotic material including a degenerated intervertebral disk, which was lying free, anterior to the vertebra. The anterior aspects of the vertebras were roughened and eroded, but no definite sequestrum could be felt or seen. The wound was drained with soft-walled tubes and left open except for the lower edge, which was loosely approximated. Cultures of the pus removed from the retroesophageal abscess revealed *Esch. coli* only. Culture and hamster inoculation were negative for acid-fast bacilli. Postoperatively, the

patient was given penicillin parenterally and penicillin irrigations locally. Thirty-five days after operation the wound had ceased to drain. The Crutchfield tongs were removed, and the patient was immobilized in a plaster jacket that included the head and neck. Approximately 4 months after operation he was placed in an adjustable supporting collar, which he wore for 11 months until the vertebras were solidly fused (Fig. 2).

The patient was followed by the Urological Service. On cystoscopy he was found to have a contracted bladder neck with a median bar and a residual urine of 50 to 100 cc. Both kidneys were normal anatomically, as demonstrated by retrograde pyelograms, and both showed good phenolsulfonphthalein excretion. Both kidneys harbored *Esch. coli*, which

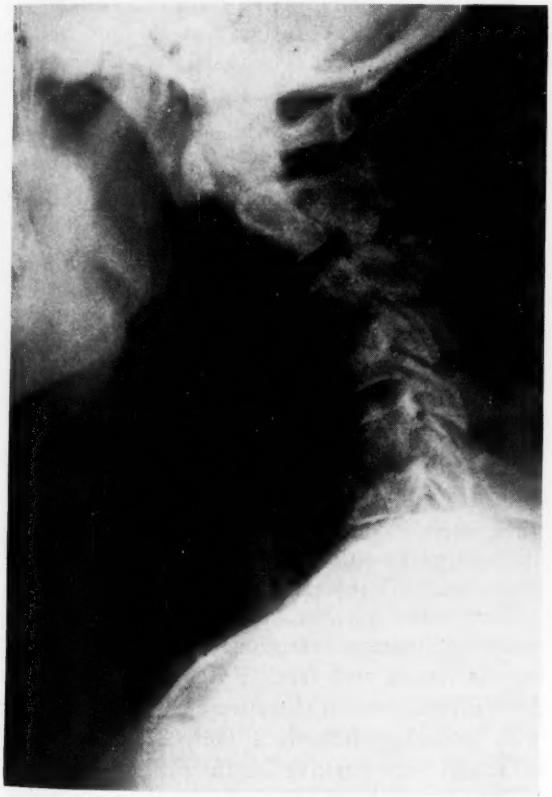

FIGURE 1. *Lateral Film of the Neck Taken on January 27, Revealing Widening of the Retrotracheal Space and Destruction of the Bodies of the Third, Fourth, Fifth and Sixth Cervical Vertebras.*

was resistant to 100 microgm. of streptomycin per cubic centimeter. He was given a 4-day course of sulfadiazine and a prolonged course of methenamine and sodium acid phosphate. Because of persistent residual urine after voiding, a transurethral resection of the bladder neck was performed in June. One month postoperatively, a right epididymitis developed, necessitating an epididymectomy 3 weeks later. Subsequently, the urine became sterile, and the patient had no further urinary complaints.

DISCUSSION

It is highly probable that the rapidly developing osteomyelitis of the cervical vertebras was secondary to the long-standing urinary-tract infection. *Esch. coli* was the sole organism cultured from both sites. The osteomyelitis did not respond to penicillin or streptomycin therapy but subsided rapidly after drainage of the abscess in the prevertebral space, removal of the necrotic intervertebral disk and immobilization. The urinary-tract infection was also resistant to treatment until a transurethral prostatic

FIGURE 2. *Lateral Film of the Neck Taken on April 4, Revealing a Normal Retrotracheal Space and a Fusion of the Third and Fourth and Fifth and Sixth Cervical Vertebras.*

resection was performed. After this procedure, there was no residual urine, and the infection disappeared.

SUMMARY

A case of metastatic osteomyelitis from a urinary-tract infection — a rare condition — is presented. Adequate open drainage and prolonged immobilization were followed by clinical improvement and later by fusion of the cervical vertebras. The urinary-tract infection was controlled only after correction of the bladder-neck obstruction.

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FUNGOUS DISEASES IN THE BOSTON AREA*

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BOSTON

THE activity of Boston dermatologists interested in mycology is probably the reason why Boston has not had the widespread epidemic of tinea capitis prevalent in most of the country. Boston is fortunate because of the rarity of deep-seated fungous infections in this section. The percentage of positive findings on patients presenting cutaneous disturbances has remained fairly constant in the last ten years, except that there has been an increase in scalp infections due to the fungi of human origin — namely, *Microsporum audouini*.

During the year 1949 routine tissue removal, direct examination and cultures were made on 829 patients presenting mycotic-like infections of the skin. One hundred and eighty-six showed positive findings by direct examination and culture. There were 21 characteristic cultures with submerged growth identifying so-called yeast-like organisms called candida. Transplanting to cornmeal agar proved 16 of these to be *Candida albicans* with characteristic chlamydospores. The remaining 5 cultures were *C. krussei* (2 cases); *C. stellatoidea* (2 cases); and *C. tropicalis* (1 case).

A predominance of the human type of fungous infection of the scalp was shown by the finding of 47 cases of *M. audouini* in contrast with 29 cases of *M. lanosum*. A rather rare finding was *Trichophyton violaceum*, isolated from a patch of tinea capitis on the scalp of a small blonde girl. The complete cultural work for the year 1949 is presented in Table 1.

Table 1. *Types of Fungi and Areas Affected.*

Fungus	Scalp	Face	Body	Chest	Arms	Hands	Legs	Feet	Nails	Total
	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	no. of cases
M. furfur			5	3	2					10
M. lanosum	29	18	6	9	9		2			73
M. audouini	47	4		1	1		1			54
M. fulvum	1	2	1				1			5
T. gypseum							1	7		8
T. rubrum		1	2		2	6	1	5		17
T. violaceum	1									1
Epidermophyton inguinale							2			2
C. albicans				2		9		4	1	16

The largest number of unconfirmed clinical diagnoses of fungous infections were those occurring on the hands and feet. Patch tests and cultures proved that most of these were contact dermatitides with secondary infection. Only 22 per cent of the scrapings were positive for fungi.

The diagnosis of fungous infection of the skin is readily made, usually by means of proper history and laboratory work. This is important because treatment of a contact dermatitis with strong antifungicides is apt to be disastrous. Proper identification of the causative fungus determines the method of treatment and the prognosis.

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MEDICAL PROGRESS

TUBERCULOSIS (Concluded)

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Para-aminosalicylic acid. It now appears that para-aminosalicylic acid (PAS) has a real place in the treatment of tuberculosis; for the first time physicians have a synthetic drug that has proved its worth in combating this disease. The original work was done in Sweden by Lehmann,[70] who has given excellent reviews of the results obtained. Practically everyone agrees that it is not as effective as streptomycin. For instance, it has practically no curative effect on tuberculous meningitis. But in other conditions it is effective alone, and is especially effective if combined with streptomycin.[71] It is given by mouth, usually in 3-gm. doses, four times a day. In this country it is being used alone in cases in which a resistance to streptomycin has already developed, but is regarded as particularly useful if given in association with streptomycin in that it delays the emergence of resistant forms of tubercle bacilli. At the end of one hundred and twenty days of treatment with streptomycin and PAS only 30 per cent of patients who have positive cultures are resistant, whereas without PAS about 80 per cent will be resistant.[38] There is, however, no hope that it prevents indefinitely the development of resistance. D'Esopo et al.[72] have shown that when no tubercle bacilli, or only sensitive bacilli, could be recovered at the end of combined treatment the bacilli could often be obtained in later cultures and were then of the resistant variety.

There are several preliminary reports from Veterans Administration hospitals showing that if the tubercle bacilli become resistant to streptomycin the addition of PAS to the treatment may cause a quick reversal to sensitive forms.

Lehmann's[70] report on the results in 205 cases of pulmonary tuberculosis treated with PAS alone and compared with 223 cases treated with streptomycin alone is summarized in Table 4. He writes, "As a *general conclusion* of this comparison between the two drugs, it must be said that their effect on the symptoms are somewhat different, the streptomycin appearing to dominate in the x-ray findings whereas PAS dominates in its effects on temperature and sedimentation rate and seems to give more stable after-treatment results."

A committee of the Swedish National Association[73] against tuberculosis reports on the favorable effects of PAS in a controlled series of 94 treated and 82 untreated cases.

The experience of the Veterans Administration in this country,[38] where PAS has been given in streptomycin-resistant cases, does not give as favorable a picture, but since this group has already been treated unsatisfactorily with streptomycin it is perhaps not one that will give a fair comparison. However, of 56 such patients given PAS, only 8.2 per cent showed moderate or marked roentgenologic improvement, as compared with 40.9 per cent of 132 treated at the same time, and for the first time, with streptomycin.

The December, 1949 ("Chemotherapy and Antibiotics Issue"), number of *Diseases of the Chest* gives good summaries of many phases of this problem.

Bogen et al.[74] have presented an excellent review of the PAS treatment of tuberculosis, with the historical background, pharmacologic aspects, animal experimentation, clinical results and a bibliography of 182 references. Hug, Moeschlin and Tanner,[75] of Zurich, report definite improvement in bronchial and renal tuberculosis as well as in 49 patients with pulmonary tuberculosis. Nagley and Logg[76] write in England on the successful treatment, with PAS alone, of 37 cases with exudative disease. Karlson et al.,[77] of the Mayo Clinic, report favorably on the use of *Promin in addition to* streptomycin and PAS as a means of delaying resistance. PAS has been given as an aerosol in the form of 1 cc. of 20 per cent solution in distilled water.[78] The only claim for the cure of tuberculous meningitis by PAS comes from Paraf[79] in France. He gave the drug *intravenously* in cases of meningitis that had become resistant to streptomycin, and reported clinical recovery in 6 patients.

There are studies now going on with daily doses of PAS up to 24 gm., and Boger and his associates[80]

TABLE 4. *Results of PAS as Compared with Streptomycin Therapy of Pulmonary Tuberculosis.*

RESULT	PATIENTS TREATED WITH STREPTOMYCIN	PATIENTS TREATED WITH PAS
	%	%
Normal temperature	47.0	75.0
Lowered sedimentation rate	51.0	84.0
Gain in weight	84.0	62.0
Sputum conversion	43.0	28.0
Progression during treatment	8.8	7.8
Cavity disappearance	23.8	18.3
Continued improvement after treatment	35.0	58.0

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have reported on a benzoic acid derivative that is said to increase the blood level of PAS as caronamide does that of penicillin.

TB1. (TbI/698. Tibione. Contiben. Myvizone). Domagk, of sulfonamide fame, has now developed this 4-aminoacetylbenzaldehyde thiosemicarbazone, which has apparently given good results in tuberculosis. No one claims that it is as effective as streptomycin. It seems to have a therapeutic rating about like that of PAS. Also like PAS, it is not effective in tuberculous meningitis. In spite of its wide use in Germany there is still reason to regard it as a drug with greater toxic dangers than either streptomycin or PAS.

The January, 1950, issue of the *American Review of Tuberculosis* has four illuminating articles on TB1. The most important is the report by Hinshaw and McDermott.[81] These highly competent American observers had the opportunity, in September, 1949, of reviewing the results obtained at ten German institutions, in the previous two years, in the treatment of 2000 patients. This group was selected from some 7000 (possibly 10,000) patients treated in more than three hundred German hospitals. The American investigators report that the initial dose should be 50 mg., by mouth, per day, for one or two weeks, with increase to 100 (possibly 200) mg. per day, and continued for six months. They say further that in one series jaundice appeared in 17 per cent of 197 treated patients and in only 6 per cent of 189 untreated patients in the same situation. Agranulocytosis occurred in 8 of the 2000 patients whose records were studied and was fatal in 1 of these, but was possibly due in some of the cases to associated administration of aminopyrine. Hemolytic crises were reported but were thought to be due usually to the large doses given in early trials and to be rare with present dosage. There is an early impressive decrease in the sedimentation rate, but this is probably a nonspecific effect of questionable clinical importance. Hinshaw and McDermott are loath to try to evaluate the efficiency of TB1 on pulmonary tuberculosis in Germany particularly "when studies in a disease like tuberculosis are made during a period of rapidly ascending quality of general medical care and nutrition." However, the Germans themselves believe that they find evidence of decided benefit in some 50 per cent of cases treated. Excellent results seem to be obtained in laryngeal tuberculosis and tuberculous enteritis. Good results are reported in tuberculous empyema, genitourinary tuberculosis and tuberculous sinuses. "No studies have been made to determine if Conteben (Tibione) administered with streptomycin will delay the emergence of streptomycin-resistant bacilli."

Mertens and Bunge,[82] two German investigators writing in the same issue, give conclusions much like those of Hinshaw and McDermott. This article has a bibliography of 97 references to the German literature on the drug.

The *British Journal of Pharmacology* for September, 1949, has two articles on the thiosemicarbazones.[83, 84] Donovick and Bernstein[85] report on the action of thiosemicarbazones in experimental tuberculosis in the mouse.

In spite of all these rather favorable comments from foreign countries the experience in this country to date has not been encouraging.

On April 25, 1950, the National Tuberculosis Association issued the following warning against the use of tibione:

> The use of TB-1 in the treatment of tuberculosis has not yet been fully evaluated by investigators in this country. Sufficient work has been done, however, to indicate that serious toxic manifestations can arise at any time during treatment with this drug. The more serious toxic effects are damage to the liver, disturbances in the blood with severe anemia or a drop in the white blood cell count or both.
>
> Some of the more readily apparent side effects are loss of appetite, nausea and vomiting, and skin rashes. In approximately 25 per cent of patients who have been given TB-1 physicians have been forced to discontinue its use because of such toxic manifestations.
>
> Toxic manifestations may occur at any time during the course of treatment and are often abrupt and without obvious warning, so that only through proper laboratory tests can their impending development be detected.

A recent preliminary summary of results from 23 hospitals in the United States on 297 patients show that 41 had changes in liver function, 34 had severe gastrointestinal disturbance, 28 showed moderate or severe anemia, and 4 had dermatitis. The liver changes, however, were quickly reversible.

Other Antobiotics

Neomycin, developed by Waksman,[86, 87] the discoverer of streptomycin, was at one time thought to be the longed-for antibiotic that would inhibit the growth of tubercle bacilli without the development of resistant forms. But the Laboratory Committee of the American Trudeau Society reported[88] on April 22, 1950, that tubercle bacilli do become resistant to neomycin in vitro; that the drug is not as effective as streptomycin against experimental tuberculosis in animals; and that different batches vary in composition and toxicity. In general it appears that neomycin is more toxic and less effective than streptomycin. *Chloromycetin* has been shown by Youmans et al.[89] to be only moderately bacteriostatic for the virulent human type of tubercle bacilli in vitro and in mice. *Aureomycin* has been proved not to be of value in tuberculosis by Steenken and Wolinsky,[90] Steinbach, Dooneief and Buchberg,[91] Rake and Donovick,[92] Perry[93] and Schwartz, Walton and Moyer.[94] *Mycomycin* is said to be effective but to present serious pharmacologic problems. *Terramycin* is being extensively studied in eighteen Veterans Administration hospitals and many other places, but it offers little promise in the treatment of tuberculosis. The dose now recom-

mended is 7.5 gm. a day. *Combined streptomycin and potassium iodide therapy.* Woody and Avery,[95] of the Department of Pathology, Vanderbilt University School of Medicine, reasoned that, since Jolling and Petersen had shown that iodides lead to the solution of caseous material in tuberculous foci, tubercle bacilli would thereby be better exposed to therapeutic agents such as streptomycin. In their experiment, at the end of fifteen weeks after infection, all the control animals were dead; 6 of 13 streptomycin-treated animals were dead; and only 2 of 14 animals who had received both streptomycin and potassium iodide were dead. The clinical trials that were started as a result of this experiment were reported (Ninth Streptomycin Conference, St. Louis) as showing that 47 patients had streptomycin and 2.3 to 5.0 gm. (35 to 75 gr.) of potassium iodide per day and did no better than 27 cases on streptomycin alone. *Sulphetrone.* Madigan,[96] Brownlee[97] and Smith et al.[98] report on the pharmacology and moderate therapeutic successes.

Nocardia extracts contain a tuberculostatic substance effective in mice, but the unpurified substance is too toxic for present use.[99] *Enniatine* is a "promising agent against acid-fast organisms but is irritating in its present form."[100] *Lupulon*, which is obtained by crystallization from a petroleum ether extract of hops, inhibits the growth of the tubercle bacillus. Chin and his associates[101] have proved its value in mice infected with the human strain and believe its action to be due to its fat solubility and consequent absorption by the lipid fraction of the tubercle bacillus. *Asiaticoside* is a purified extract from a plant, *Centella asiatica*, which natives have used in the treatment of leprosy. Boiteau and Saracino[102] report good results in experimental tuberculosis in the guinea pig, and in 8 cases of lupus in human beings. *Usnic acid* is stated by Marshak and Kuschner[103] to retard the development of tuberculosis in guinea pigs if combined with low doses of streptomycin; usnic acid alone has no effect. *Nicotinic acid amide.* McKenzie et al.[104] found that this chemical markedly suppressed the spread of tuberculosis in infected white mice but that calculated on a weight basis from the results in mice the dose could not be tolerated by human beings. *Neohetramine.* In these days of antihistamine tryouts it is natural to use such drugs in experimental tuberculosis. Duca and Scudi[105] gave Neohetramine twice daily to 20 guinea pigs previously infected with tubercle bacilli. A like number of infected guinea pigs were kept as controls. In the treated animals the disease was more chronic, the tubercles showing more fibrosis and lymphocytosis, and they had approximately half as much gross tuberculosis. The authors suggested that Neohetramine be used in combination with streptomycin for exudative tuberculosis. *ACTH.* An abstract of a paper by Tompsett et al.[106] presented before the American Society for Clinical Investigation reads as follows:

> An investigation has been made of the effects of ACTH in patients with advanced tuberculosis, with particular reference to the acute manifestations of the illness and the evolution of visible tuberculous lesions (laryngeal).
>
> In four subjects studied thus far, the administration of ACTH (100 mg. daily) has been followed within six to eight hours by amelioration and subsequent rapid disappearance of the systemic manifestations of acute illness. Complete defervescence has been accompanied by marked improvement in strength, appetite, and phonation, and by loss of previous cutaneous hypersensitivity to tuberculin. The onset of visible changes in the laryngeal lesions occurred within 24 hours and were increasingly evident thereafter. Laryngeal edema receded, granulations became less elevated and were covered with epidermis.
>
> Sudden withdrawal of ACTH after a short period of administration was followed by the abrupt return of all previous signs of acute illness without return of the laryngeal ulcerations. Study of more prolonged ACTH administration in additional patients is in progress. Whether the ultimate effect of ACTH on the extensive pulmonary lesions of these subjects will be beneficial or adverse, is as yet unclear.
>
> Regardless of ultimate outcome, it has clearly been possible to abolish the evidences of tuberculous illness by the administration of a substance which presumably acts solely on the host. Thus the present results with ACTH in a protracted destructive infection are comparable to Finland's previous observations in acute non-tuberculous pneumonias.

Surgery of Tuberculosis

There are today three problems of especial interest in the surgery of tuberculosis: the present status of thoracoplasty; the place of excision therapy in pulmonary tuberculosis and the influence of streptomycin in encouraging such an operative procedure; and the value of decortication of lungs bound down by organized or partially organized tuberculous exudate.

So far as thoracoplasty is concerned it is still in most cases the operation of choice. Kinsella et al.,[107] at Glen Lake Sanatorium, report on thoracoplasties in 613 patients performed from 1922 to 1943. Sixty-seven per cent are alive, five to twenty-six years after operation. Since 1931 the postoperative mortality in the first eight weeks has been 3 per cent. Rubin and Klopstock,[108] of Triboro Hospital, discuss 141 thoracoplasties, done two to six years previously, with an operative mortality of 5.3 per cent and an over-all mortality of 14.2 per cent. The best results were obtained in unilateral, fibrocaseous tuberculosis. Giant thin-walled cavities, thick-walled cavities and tuberculosis with bronchiectasis accounted for most of the failures. Reports like these do much to keep up one's faith in the time-honored operation of thoracoplasty.

However, pulmonary resection is again growing in favor. The early enthusiasm was followed by a period of concern lest the disease left behind in the remaining lobes on the operated side, or in the opposite lung in case of pneumonectomy, become activated. But refinements in surgical technic and the protection of streptomycin have given the surgeon

new courage, and more and more "successful" series of resections are being reported. Most thoracic surgeons do a partial thoracoplasty after such an excision to prevent the development of "compensatory emphysema," which they regard as one cause of activation of foci left behind.

One should look first at a series of resections done in the days before streptomycin was available. Sweet[109] now publishes a "subsequent report" on his series of 27 lobectomies and 36 pneumonectomies done before the streptomycin days. It is now three or more years since the operations. Of a total of 63 patients operated on 9 died shortly after operation, and 19 died subsequently. Nine patients are alive with active disease. Seven patients had active disease but are now well, and 19 patients have continued to be well. Sweet concludes that "approximately two-thirds have manifested some form of late activity of persistent foci of disease." In the pneumonectomy group there was late tuberculous empyema in 4 cases, 2 with fistulas. Sweet makes the further statement:

> The indications for extirpative surgery at the present time are (1) irreversible bronchostenosis with chronic infection and secondary bronchiectatic dilatation, (2) lower lobe (or occasionally middle lobe) cavities, (3) persistent cavity after adequate thoracoplasty, and (4) possibly tuberculoma. Cases suitable for thoracoplasty are no longer considered for extirpation.

In the second place are reported series in which the results of excision under streptomycin protection are compared with results before streptomycin.

Murphy,[110] at the Veterans Administration Hospital in Oteen, North Carolina, says that, before streptomycin, resection carried a mortality of 25 per cent and an incidence of empyema of 12 per cent and of bronchopleural fistula of 8 per cent.

TABLE 5. *Figures on Resections.*

STREPTOMYCIN STATUS	NO. OF RESECTIONS	PERCENTAGE OF SPREADS
No previous streptomycin	331	11
Organism resistant to streptomycin	59	82
Organism sensitive to streptomycin	108	70
Sensitivity unknown	119	72

He then describes a series of 129 resections (77 lobectomies and 52 pneumonectomies) done under streptomycin protection with a mortality of 4.5 per cent and an incidence of empyema of 4 per cent.

Mulvihill et al.[111] at the Triboro Hospital, report that, before streptomycin, in 21 lobectomies there were 3 deaths in nine months from bronchopleural fistulas, empyema and contralateral spread. Since streptomycin there have been 13 resections, and no such complications.

Bailey, Glover and O'Neill[112] (Philadelphia) compare 100 cases of resection for pulmonary tuberculosis without streptomycin with 100 in which streptomycin was used. They had 15 per cent of postoperative spreads without streptomycin and only 1 per cent with streptomycin.

Moore, Murphy and Elrod,[113] at the Veterans Administration Hospital in Oteen, North Carolina, compare 11 resections without streptomycin with 74 resections with streptomycin. The mortality has been reduced from 36 to 8.1 per cent, the rate of spreads from 27 to 4 per cent, and the rate of fistulas and empyemas from 55 to 5 per cent, and the sputum conversion has risen from 58 to 87 per cent.

Thirdly is the problem of resection in a patient who has had one or more *full* courses of streptomycin in the past, and not just a protective dose for about a week before excision and two weeks after. If such a candidate for resection is proved to be carrying resistant tubercle bacilli the surgeon is loath to do the operation, and it is on this account that he so often pleads that under ordinary conditions the drug be withheld, so as to give protection if excisional therapy is indicated later. But recent studies make one suspicious that even when resistant bacilli have not been reported the patient previously treated with streptomycin is a worse surgical risk than one who has not been so treated.

The consolidated figures on resections compiled from the tables of the Ninth Veterans Administration Streptomycin Conference, April, 1950, are presented in Table 5.

Finally, it is interesting to note that even in the patients who had not previously received courses of streptomycin and who were given only protective streptomycin at the time of excision the percentage of spreads and other complications has increased in recent months. An early series of resections done under these conditions resulted in only 2.2 per cent of spreads in 87 lobectomies and 3.8 per cent in 54 pneumonectomies, as compared with the 9.6 per cent in lobectomies and the 10.5 per cent in pneumonectomies noted above. It seems probable that poorer risks are being accepted for resection.

The great success obtained in *decortications* after war injuries of the chest led the thoracic surgeons to see whether equally good results might be achieved with tuberculous pleural exudates, particularly with the tuberculous empyemas, which are all too common after artificial pneumothorax. It has now been shown that a complete pleural "sac" composed of organized exudate outside both the visceral and parietal pleura can be "peeled" off with comparative safety and that the lung will then often re-expand. Its functional capacity, however, may still be very low.

O'Rourke, O'Brien and Tuttle[114] (Detroit) describe 43 decortications for pulmonary and pleural tuberculosis performed between January, 1946, and May, 1948. There were 9 patients with tuberculous pleurisy, 27 with complications of thera-

peutic pneumothorax and 7 with lobectomy in conjunction with decortication. The respective results were failure in 4, improved in 5, good in 14 and excellent in 20.

Mulvihill and Klopstock,[115] at the Triboro Hospital, report 5 cases of successful surgical re-expansion of postpneumothorax, nonexpandable lung.

Weinberg and Davis,[116] at the Veterans Administration Hospital in Van Nuys, California, had 15 patients with unexpandable lung and persistent pleural space after unsuccessful pneumothorax treated by total or almost total decortication. There were no deaths and no case of spread of pulmonary tuberculosis. Four patients had thoracoplasties in addition. There was an immediate postoperative decrease in total pulmonary function, with an appreciable increase in function after several months.

Gordon and Welles,[117] of Saranac Lake, New York, report in detail on 9 cases of decortication.

Wright et al.[118] raise a further question concerning the unpredictable amount of function in the re-expanded lung.

BCG Immunization

The experience with BCG in this country and in Scandinavia was reviewed by Wassersug[119] last year. An excellent summary of the experience with BCG all over the world, with arguments pro and con, was presented by Edsall.[120]

It should be noted that in the November, 1949, issue of the *American Review of Tuberculosis* the American Trudeau Society, through its Committee on Medical Research and Therapy, and its Subcommittee on Immunology, published a "Statement on BCG,"[121, 122] which had been adopted by the Council. This report may be summarized as follows.

Under acceptable conditions the vaccine is "harmless."

The degree of protection is "by no means complete," nor is the duration predictable.[123]

Vaccination is recommended for "the following more vulnerable groups," "provided they do not react to adequate tuberculin tests."

Doctors, medical students and nurses who are exposed to tuberculosis.

Hospital and laboratory personnel.

Those unavoidably exposed in the home.

Patients and employees of mental hospitals and custodial institutions.

"Children and certain adults considered to have inferior resistance and living in communities in which the tuberculosis mortality rate is unusually high."

Efforts are recommended to "meet in practice suitable standards for the production of BCG vaccine, and that, when practicable, commercial firms be licensed under the National Institute of Health to produce this vaccine."

It is believed that there are other, more effective methods of controlling tuberculosis in the general population than BCG vaccination.

Vaccination is only one of many procedures to be used in tuberculosis control.

Expansion of other facilities is required.

In the United States 6596 vaccinations were performed in New York State in 1948 and 1949, and 3438 in Pennsylvania from July 1, 1949 to January 28, 1950; 168,272 doses were distributed by Chicago laboratories up to the end of 1949[124]; and 1400 inoculations had been given in Massachusetts up to the end of 1949.[125]

There is a strong movement on foot to prepare a stable *dried* BCG vaccine.[124]

The experiences with BCG in Norway have been summarized in a 224-page book in English by Dr. Gerhard Hertzberg.[126]

BCG vaccination is now compulsory for certain groups in France,[127] Norway[128] and Brazil.[129]

Conclusions

Mortality

Between 1900 and 1948 the death rate from tuberculosis in the United States dropped from 202 per 100,000 population to 30. In Massachusetts the drop was from 253 to 29.6. Instead of being first in the list of causes of death, tuberculosis is now seventh. However, it is still the leading cause of death among those who die between the ages of fifteen and thirty-five. The age at which death from tuberculosis occurs is steadily advancing. "Rest, fresh air, and good food" was the formula for treatment in 1900. Since that time treatment by artificial pneumothorax and pneumoperitoneum, surgical "compression" therapy, surgical excision and, recently, chemotherapy have been added.

Mass surveys

Mass x-ray surveys of the supposedly well are being conducted in many large cities throughout the United States in the hope that active pulmonary tuberculosis will be discovered before it gives symptoms and while treatment may offer hope of a permanent cure. Only about one tenth of 1 per cent of the total number of persons receiving x-ray examinations have eventually been proved to have active pulmonary tuberculosis, instead of the 1 per cent previously expected. The final results of the Boston X-Ray Survey are not yet available, but preliminary reports show that seven one-hundredths of 1 per cent of the Boston residents examined have been proved to have active pulmonary tuberculosis. When such a city-wide x-ray survey is planned provision should be made beforehand for the prompt and efficient care of the active cases that may be discovered. On the whole such studies are worth while, but one must keep in mind their limitations and dangers.

Tests for Activity

Less than half the cases of active pulmonary tuberculosis produce a sputum showing tubercle bacilli on direct smear. Cultures or guinea-pig inoculation of the *sputum* give a marked increase in positive findings, and when there is no sputum a surprisingly high percentage of specimens of *gastric contents* will give a positive culture. The more careful the technic and the larger the number of specimens examined, the higher the percentage. It is enlightening, for instance, to find that in 15 nurses whose tuberculin tests had changed from negative to positive there was a positive gastric culture, with guinea-pig confirmation, and that in 8 of the 15 the x-ray film disclosed no disease. These experiences show that culture of the gastric contents is an important way to determine the activity of pulmonary tuberculosis. But it is becoming more and more difficult to decide how often to do such gastric cultures and how much stress to place on the *occasional* positive reaction in a patient who is clinically well and whose x-ray shadows do not look like those of active disease. Good judgment is required.

Many new blood serum tests are being devised in the hope that they will help determine activity. So far none of these tests, including the frequently mentioned hemagglutinin test of Middlebrook and Dubos, offers real hope. In a consideration of this problem it must be kept in mind that there is never going to be a sharp line of demarkation between activity and nonactivity. There will be every grade of activity from that of almost healed fibrotic disease to the very active case with fever and night sweats.

Antibiotics

Streptomycin. After four years of the most extensive study by the Veterans Administration with the Army and Navy, the American Trudeau Society and the United States Public Health Service, not to mention a host of individual observers, streptomycin has proved itself to be a very valuable adjunct to bed rest, collapse therapy and the surgery of pulmonary tuberculosis. It is not a cure-all for the disease. In most cases it will do much to clear the "exudative component" of a pulmonary tuberculous infection, but it has little effect on fibrocavernous disease except to promote better bronchial drainage in the presence of tuberculous infection of the bronchial wall. It is extremely helpful in relieving the symptoms of laryngeal, pharyngeal and intestinal tuberculosis, and many other extrapulmonary infections. The orthopedists and genitourinary specialists find it very valuable. It has saved some lives in patients with tuberculous meningitis — a disease hitherto 100 hundred per cent fatal.

The principal difficulty in the use of streptomycin has been that about 50 per cent of the cases continue to have positive sputums even after a four-month period of treatment, and that 80 per cent of the cultures of such sputums show streptomycin-resistant tubercle bacilli. To prevent this development of resistance the period of treatment has often been shortened, but though there are only 35 per cent resistant bacilli at the end of six weeks, there is a loss of therapeutic effect. Recently, the combination of para-aminosalicylic acid (PAS) and streptomycin has done much to delay the development of resistance, and in almost every case in which streptomycin is being given PAS is now added. In such cases only 30 per cent of the positive cultures are resistant at the end of four months. A change in the dosage schedule is being adopted by many hospitals, largely as a result of the experience at the Fitzsimons General Hospital of the Army, and if one reviews carefully all the available reports on streptomycin therapy it looks as if the treatment of choice today was 1 gm. of streptomycin twice a week, instead of daily injections, and 3 gm. of PAS given four times each day. This treatment should usually be continued for four months or longer.

Dihydrostreptomycin. There is some difference of opinion among good authorities about the relative merits of dihydrostreptomycin and regular streptomycin. There are still those who fear the emergence of delayed deafness even with a 1-gm. daily dosage of dihydrostreptomycin sulfate, although others claim that the deafness has occurred only in patients who are getting 3 gm. of the dihydrostreptomycin hydrochloride daily. Streptomycin is the drug of choice.

Para-aminosalicylic acid. Besides its relation to streptomycin resistance this drug is valuable when used alone. It is being tried extensively in patients who have had previous streptomycin treatment with resulting streptomycin-resistant bacilli. In effective dosage it often has unpleasant gastrointestinal effects.

Tibione. Although widely heralded in Germany as a new treatment for tuberculosis the studies so far conducted in this country show that the drug is less effective than streptomycin or PAS and that it has dangerous toxic potentialities for the blood and liver. Although the small dose of 100 to 200 mg. per day is easier to take than the 12 gm. or more of PAS, the gastrointestinal disturbances after tibione are apparently as great. At present there is no reason for using tibione if streptomycin or PAS is available.

None of the other antibiotics that are receiving extensive investigation are very promising. As in many other conditions ACTH gives early strange and wonderful changes.

Surgery of Tuberculosis

Thoracoplasty continues to be the operation of choice, and the end results of this procedure are still very satisfactory. The surgeons are at work on many modifications.

The excision of tuberculous foci from the lungs has been proved to be technically feasible, and the temptation to "cut out the rotten spot" is great indeed. Before streptomycin the end results of these excisional procedures was disturbing because in many patients the disease spread in the parts of the lung that had been left behind. But with the use of streptomycin the development of these postoperative spreads has been lessened considerably, and the procedure is again becoming popular. It is difficult to interpret the comparative figures of the past few years because it is quite obvious that the surgeons are attempting excisions in more and more serious cases and the increase in the postoperative complications must be due in part to this selection. However, the figures seem to show that the patient who has never had streptomycin except at the time that the excisional surgery is practiced is a much better risk than the one who has previously had streptomycin, even when the tubercle bacilli are still sensitive. But one cannot always withhold streptomycin because the surgeon may some day want to do a resection, and the choice when to give it requires judgment on the part of both the physician and the surgeon.

BCG

There is as yet no good argument for a campaign to "immunize" with BCG all persons in this country who are negative to tuberculin. Certainly, until the vaccine has become more standardized its use should be confined to the groups most definitely exposed. Efforts are on foot to prepare a stable, dry vaccine.

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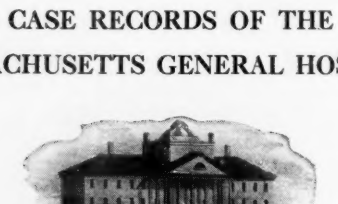
CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36411

Presentation of Case

First admission. A forty-five-year-old man entered the hospital complaining of pain in the left flank.

The patient had one attack of rheumatic fever at the age of six, following which a heart murmur was repeatedly heard. At the age of eighteen he began to have four or five attacks of bronchial asthma each year and developed chronic wheezing and dyspnea. For many years he had slept on two pillows. He habitually took a very poor diet and until one year before admission drank "three fifths" of whisky each week. Two years prior to entry he had a hemoptysis of several ounces of bright-red blood. About this time he began to have progressive impotence. One year before admission he had a severe upper respiratory infection with pulmonary congestion that cleared following penicillin. He was put on a low-salt diet and digitalis and was able to return to work although he tired easily, had increased dyspnea and lost 20 pounds in weight during the next year. Seven months before admission he noted a tender, slowly growing mass in the left breast that was removed, and the pathological report was gynecomastia. Following the operation there was a marked increase in dyspnea for which the patient was readmitted to another hospital a week after the operation. He was given a strict low-salt diet and three mercurial injections, following which he developed a skin rash, ankle edema and increased orthopnea. These gradually improved, and he was discharged home. One week before entry bilateral calf tenderness appeared. However, he did well until four days prior to admission, when there was one transient episode of diplopia and the onset of nocturia. On the following day he began to have costovertebral-angle pain, most pronounced on the left side, accompanied by urgency, frequency and oliguria. Two days before admission the pain radiated into the left flank, and dysuria was noted.

Physical examination showed an acutely ill man with Cheyne-Stokes respiration. The cardiac rhythm was grossly irregular, with an apical rate of 120. The neck veins were markedly distended. There were moist rales at both lung bases. The heart was enlarged to the anterior axillary line. The pulmonic second sound was much louder than the aortic. A Grade II systolic murmur was heard at the apex. A tender liver was palpated three fingerbreadths below the costal margin. Left-costovertebral-angle tenderness was pronounced. There was slight bilateral calf tenderness, but Homans's sign was negative.

The temperature was 102°F., and the pulse 90. The blood pressure was 131 systolic, 90 diastolic.

The urine had a specific gravity of 1.026 and gave a ++ test for albumin, and the sediment contained 5 white cells and 4 red cells per high-power field. Five subsequent specimens were similar, and one was loaded with red cells. No organisms were demonstrated on smear or by culture. Examination of the blood disclosed a hemoglobin of 16.5 gm. and a white-cell count of 35,100, with 93 per cent neutrophils. A blood Hinton test was negative. A stool was guaiac negative. Repeated blood cultures were negative. The corrected sedimentation rate was 0.7 mm. per minute. The circulation time was 30 seconds. The nonprotein nitrogen was 56 mg., the total protein 5.6 gm., the calcium 9.8 mg., the phosphorus 2.2 mg., the alkaline phosphatase 6.0 units, and the van den Bergh reactions 2.8 mg.

direct and 4.2 mg. total per 100 cc., the prothrombin time 63 per cent of normal, the carbon dioxide 30.8 milliequiv., the chloride 97 milliequiv., the sodium 136 milliequiv., and the potassium 5.8 milliequiv. per liter, and the blood pH 7.3. An electrocardiogram showed auricular fibrillation at a rate of 100, right-axis deviation and sagging ST segments. X-ray films disclosed enlargement of the left auricle and ventricle and a calcified aorta. Intravenous retrograde pyelograms taken in the third week of the hospital course demonstrated a very small, nonfunctioning left kidney of normal outline and a large, functioning right kidney with the suggestion of a mass in the lateral midportion.

The patient was maintained on 0.2 mg. of digitoxin per day throughout most of the hospital course. Following repeated Mercuhydrin injections the weight dropped 10 pounds, remaining stable during the last week of admission with a 2-cc. injection every other day. In the first nine days of the hospital course he received 10 gm. of streptomycin, and for the first eighteen days Crysticillin. The temperature remained normal after the fifth day, but the fibrillation and tachycardia persisted. The most acute subjective problem throughout most of the course was persistent hiccuping, which failed to respond to carbon dioxide inhalation, intravenous administration of calcium gluconate, sedatives, small doses of quinidine or electrical stimulation of the phrenic nerve. It was finally controlled by repeated phrenic-nerve blocks. On the third hospital day there was a sudden onset of weakness and tingling in the right forearm and right-costovertebral-angle pain radiating into the right flank. The right hand was found to be cooler than the left, with a weak right radial pulse. A diagnosis of peripheral embolism was made, and the patient was given a total of 150 mg. of heparin and 325 mg. of Dicumarol, following which the prothrombin time fell from 63 per cent of normal to less than 10 per cent on the ninth hospital day. Following 10 mg. of Hykinone, the prothrombin time rose rapidly to 41 per cent. The right arm gradually became asymptomatic, and the right-costovertebral-angle pain diminished. Following retrograde pyelography on the seventeenth hospital day there was a brief episode of mild shock and congestive failure, which cleared rapidly with routine therapy. The patient was discharged on the fortieth hospital day. He was still fibrillating at a rate of 110 and had a few moist rales at the lung bases, +++ edema to the knees, profound depression due to generalized weakness, persistent flank pain, insomnia and hiccuping.

Final admission (three weeks later). He remained at home for a week and was then transferred for two weeks to a nursing home, where he was kept on a low-salt diet, digitoxin and a mercurial injection every other day.

One week before the second admission he began to complain of substernal soreness. Four days before admission the sputum became blood streaked although there was no acute episode of any sort. There was a progressive increase in dyspnea. The patient was readmitted complaining of total insomnia for two days and incapacitating weakness.

Physical examination revealed a thin, questionably jaundiced man with severe dyspnea and orthopnea but no cyanosis. The neck veins were distended to the angle of the jaw, and there was ++++ edema of the lower legs, where some breakdown of the stretched skin was noted. There were decreased breath sounds and dullness at the right base. The heart beat was irregular at a rate of 96. A Grade II systolic murmur was heard at the apex and at the left sternal border. The liver was tender but its size could not be determined.

The temperature was 98.6°F., and the respirations 18. The blood pressure was 105 systolic, 65 diastolic.

No urine could be obtained for analysis. Examination of the blood revealed 11.0 gm. of hemoglobin and a white-cell count of 11,000, with 89 per cent neutrophils. The nonprotein nitrogen was 32 mg., and the total protein 5.0 gm. per 100 cc., and the sodium 122.7 milliequiv., the chloride 85 milliequiv., the potassium 5.3 milliequiv., and the carbon dioxide 28.3 milliequiv. per liter, and the prothrombin time 28 seconds (normal, 17 seconds), or 45 per cent of normal.

The patient was given 0.4 mg. of Cedilanid intravenously at once and put on 0.2 mg. of digitoxin a day. Since the edema was considered to be due in part to salt depletion, he was placed on an unrestricted diet with fluids ad libitum. The urinary output during the first day was only 360 cc. in spite of injection of a mercurial diuretic. The patient went rapidly downhill, with progressive edema, oliguria, dyspnea, extreme discomfort and disorientation, and died on the third hospital day.

Differential Diagnosis

Dr. Myles P. Baker*: My first impression in reading over this protocol was that this man had died in congestive heart failure as the result of long-standing rheumatic heart disease, mitral stenosis and auricular fibrillation, with the common complication of congestive heart failure, — multiple pulmonary infarctions, — and that terminally he showed both the symptoms and the pattern, in the blood chemical studies, of the low-salt syndrome.

Let us review some of the features of the past history and the outstanding points about the physical findings and the laboratory work in support of such a diagnosis or in contradiction of it. The important features in the past history seem to be the story of rheumatic fever as a youngster, secondly, the story, which I have to take at face value, of

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bronchial asthma presumably on an allergic basis that apparently continued annually up until the last illness and, thirdly, some evidence that he may have lived in such a way as to damage the liver.

The story of a hemoptysis two years prior to the first admission without a subsequent development of proved pulmonary infection makes one wonder about the possibility of pulmonary embolization and infarction. Hemoptysis does occur with long-standing mitral stenosis, of course, but I would expect more associated symptomatology of congestive heart failure in connection with this episode two years before, had this been a manifestation of rheumatic heart disease. There is a strong suggestion that a year prior to admission the patient had been considered to be in congestive heart failure and had been treated in accordance with this diagnosis. It is rather unusual that he lost so much weight during the two years prior to admission if he were on the border of cardiac failure. Just prior to admission he developed a marked increase in dyspnea following a minor surgical procedure; the ankle edema, dyspnea and orthopnea had responded rather poorly to mercurial diuretics.

Finally, the patient came in with a story again strongly suggestive of embolization as a complication of auricular fibrillation. The important physical findings were uncontrollable auricular fibrillation, with distention of neck veins, rales at the bases of the lungs, a large tender liver and tenderness in the left costovertebral angle consistent with a renal infarct. The bilateral calf tenderness is consistent with an underlying deep phlebothrombosis even though the Homans's sign was not obviously present.

The laboratory findings revealed microscopic hematuria, no evidence of urinary-tract infection, a white-cell count in keeping with infarction in either the kidneys or the lungs or both, a prolonged circulation time as one would expect in congestive failure and an elevated nonprotein nitrogen, which is in keeping with the presence of a fresh renal infarct and congestive heart failure. The elevated bilirubinemia, even without any evidence of jaundice in the presence of congestive heart failure, makes one consider at least the presence of infarction, usually pulmonary, which allows for the presentation to the liver of more blood pigment than it can excrete in the form of bilirubin. The electrocardiogram did not help me much. I take it these sagging ST segments were digitalis effects. X-ray films revealed an enlargement of the left auricle and ventricle, as Dr. Wyman can perhaps show us later. I should think the left auricular enlargement would be important in the differential diagnosis.

The first important thing that happened to this man following admission was the development of symptoms of embolization of the arteries in the right forearm and also repeated embolization and probably infarction in the right-kidney region. The second important feature in the course was the persistent hiccuping, which seemed to require a diagnostic explanation. Hiccuping in a patient with congestive heart failure is to me explicable on the basis of repeated pulmonary infarction with irritation of the diaphragm. I have seen this in similar cases.

The fourth important feature of the hospital stay was the persistence of a rapid ventricular rate in a man with fibrillation who was not running an elevated temperature and who was receiving what should have been an adequate daily maintenance dose of digitoxin. That, in the absence of obvious infection, should make the physicians consider the presence of infarcts, usually pulmonary.

May we see the x-ray films?

Dr. Stanley M. Wyman: The original chest films show the lung fields to be grossly clear, but there is considerable enlargement of the heart toward the left. This appears to involve the left ventricle and also the right ventricle, which lies in apposition with the sternum for a long distance as seen in the lateral view. The hilar and pulmonary vascular shadows are definitely increased in prominence, and there is calcification in the aorta. The last set of films of the chest were taken three weeks later, and this time the film is upright and therefore shows a more nearly accurate representation of the heart, which again is seen to be enlarged in the region of the ventricles and probably the left auricle, which extends back in this region. There is no pleural effusion on the right, but there is still further engorgement of the vascular bed probably with pulmonary edema and possibly with pneumonitis. The next two sets of films were taken, I imagine, shortly before death, and they were all taken in the supine position. The effusion in the right chest has increased considerably, and there is a large density in the left mid-lung field somewhat laterally and a smaller density in the right mid-lung field, which, as Dr. Baker suggested, are consistent with infarcts. On the last study there appears to be a large amount of pulmonary edema in both mid-lung fields.

Dr. Baker: Is there anything to be said about the films of the kidneys, Dr. Wyman?

Dr. Wyman: Yes, indeed. The films of the kidneys were all done between the first two chest examinations. The first three films are from the intravenous pyelogram, and they show a small left kidney and a rather large right kidney, which cannot be too well outlined, however. Calcification is present, probably in the mesenteric lymph nodes. There is some calcium in the abdominal aorta and its distal branches. The last film is from the retrograde pyelogram and shows grossly normal calyceal systems of the left kidney; the calyxes of the

right kidney are not remarkable. I would not be concerned about the possibility of a mass.

DR. BAKER: Thank you very much.

The details about the second and final admissions to the hospital are fairly straightforward. It seems to me important that the patient did have substernal soreness and some blood streaking of the sputum prior to admission. The absence of cyanosis is noteworthy in a person with such marked distention of the neck veins. Again, the systolic murmur heard in the apex was not particularly abnormal. At this time there was a definite lowering of the blood sodium and chloride levels; the potassium level was not impressively elevated. The low level of serum protein probably bespeaks inadequate nutrition.

Is there any chance that this man could not have had rheumatic heart disease but a chronic cor pulmonale over the last few years, perhaps as the result of long-standing bronchial asthma? Chronic cor pulmonale is a rare development in bronchial asthma. It does occur, but it seems to me rather a far cry. Could it have been a chronic cor pulmonale developing as an unusual result of repeated undetected pulmonary embolizations over the years? There is one feature that I think should be stressed — namely, that auricular fibrillation is uncommon in chronic cor pulmonale. In one series of 60 cases[1] reported from New York, only 9 patients developed auricular fibrillation, and some of these were people, older than this patient, who had some arteriosclerotic heart disease as well. The presence of an enlarged left auricle is perhaps another point in favor of rheumatic heart disease and mitral stenosis; auricular fibrillation develops in two thirds of the cases manifesting mitral-valve stenosis.

I think that I shall stick by the commonest possibilities, then, and say that the data support the diagnostic impression of rheumatic heart disease with mitral stenosis, auricular fibrillation, congestive heart failure and repeated pulmonary infarcts that were the result of embolization from the deep leg veins, not from the right chambers of the heart, and, at the end, a low-salt syndrome probably contributed to by the low intake of sodium and recent mercurial injections. Whether any specific evidence of such a syndrome can be found in the kidneys I would very much doubt.

DR. BENJAMIN CASTLEMAN: You think the oliguria was due to the low-salt syndrome?

DR. BAKER: Yes. There should have been renal infarcts in the large right kidney. I took it that the small left kidney was the result of a hypoplasia, a congenital anomaly.

DR. MARIAN W. ROPES: Those of us who saw the patient on the wards felt very much the same as Dr. Baker. We thought the patient had rheumatic heart disease and were aware of the many areas of embolization and infarctions in the lungs and presumably in the kidneys.

CLINICAL DIAGNOSES

Rheumatic heart disease, with mitral stenosis and aortic insufficiency.
Congestive heart failure.
Pulmonary and renal infarcts.

DR. BAKER'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis.
Auricular fibrillation.
Congestive heart failure.
Pulmonary infarcts, repeated.
Renal infarcts.
Low-salt syndrome.

ANATOMICAL DIAGNOSES

Rheumatic heart disease, with severe mitral and aortic stenosis.
Mural thrombus, left auricle.
Embolus of abdominal aorta, with superimposed thrombosis extending into renal arteries.
Renal infarcts, old and recent, multiple.
Pulmonary infarcts, multiple.
Central congestion and necrosis of liver.
Jaundice.
Sclerosis of abdominal aorta.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy did show a rheumatic heart, weighing 500 gm., with very severe mitral and aortic stenosis. There was a mural thrombus in the left auricle, which probably accounted for many of the peripheral emboli. The lungs also showed numerous infarcts, infarcts being present in all lobes at the time of autopsy. There was not a mural thrombus in the right auricle. Unfortunately, the leg veins were not examined, but I am fairly certain that the pulmonary emboli arose from the deep veins of the legs. The liver was markedly congested and on microscopical examination showed a good deal of central necrosis but no evidence as yet of any cardiac cirrhosis.

The kidneys were quite interesting on gross examination. I have a picture of them (Fig. 1). Overlying the intima of the abdominal aorta, including the mouths of the renal arteries and extending into both iliac vessels, is an adherent mural thrombus. It will be noticed also that there is a good deal of calcification and severe sclerosis in the abdominal aorta, which is a bit unusual in a man of forty-five. The large right kidney, which weighed 200 gm., showed some recent infarcts; the left was almost totally infarcted, with both old and recent infarctions, and the entire left renal artery was completely occluded by a thrombus. I believe that this probably represented an embolus from the left auricle that was caught at the bifurcation in the severe arteriosclerosis rather than a localized mural

thrombus, although one cannot rule that out. Since he had so many emboli in other parts of the body, it is more reasonable perhaps to assume that it was an embolus on which there was superimposed thrombus and extension into both renal arteries. I believe the small size of the kidney was due to infarction rather than to congenital hypoplasia.

DR. BAKER: Do you find anything specific in the kidneys in cardiac patients dying with low-salt syndrome?

DR. CASTLEMAN: No; we have just had a patient recently who we believe died with that syndrome,[2] and we were not able to find anything definite in the kidneys. These patients usually have an elevated nonprotein nitrogen.

FIGURE 1.

DR. BAKER: I was impressed by that figure of 32 mg. per 100 cc. of nonprotein nitrogen at the time of death; it is certainly not the rule in most of the low-sodium cases with renal insufficiency.

DR. CASTLEMAN: That would be an argument against the low-salt syndrome.

DR. BAKER: On the other hand Dr. Schroeder[3] has reported a series in which there were 2 or 3 cases with nonprotein nitrogens of about 40 or 50 mg. per 100 cc. and with very low blood sodium and chloride.

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CASE 36412

PRESENTATION OF CASE

A sixty-four-year-old woman was admitted to the hospital for the first time because of a chronic dry irritating cough.

Three years before entry the patient entered another hospital because of low-back pain and sciatica that was ascribed to a subsiding intervertebral disk and for which she received conservative orthopedic treatment with satisfactory response. At that time x-ray study revealed an abnormal shadow in the left-lung field. That was followed with chest films at frequent intervals, with no observable changes until recently. About three months prior to admission she developed easy fatigability, an occasional evening rise in temperature and night sweats. These symptoms subsided after a month but were replaced by an irritating, nonproductive cough, which persisted. Three weeks prior to admission she developed a pleuritic type of pain in the right pectoral region extending over the lower lateral aspect of the right chest. The complaint likewise subsided gradually, but the cough persisted. The appetite was considered good, and there had been no significant weight loss. Sputum examinations outside the hospital were negative for acid-fast organisms, but chest x-ray films showed an increase in size of the previously noted shadow.

A hysterectomy and appendectomy had been performed fifteen years before admission because of postmenopausal bleeding.

Physical examination revealed a fairly well nourished woman, coughing frequently but not appearing acutely or chronically ill. The lungs were clear. A single discrete, firm lymph node, 1 cm. in diameter, was palpable in each axilla. The breasts were normal. There was a well healed lower midline abdominal scar.

The temperature was 98°F., the pulse 65, and the respirations 20. The blood pressure was 180 systolic, 90 diastolic.

The urine had a specific gravity of 1.020 and gave a + test for albumin, and the sediment contained 10 leukocytes per high-power field. The hemoglobin was 11 gm. The white-cell counts ranged from 3000 to 5000, with 34 to 55 per cent neutrophils. Repeated stool examinations were guaiac negative. The sedimentation rate was 7 mm. in one hour. A blood Hinton test was negative. Chest x-ray films

(Fig. 1 and 2) showed a rounded lesion, 4 cm. in diameter, in the axillary portion of the posterior apical segment of the left upper lobe. A few nodular densities were present in the lung field proximal to this region. The lesion was located at the periphery of the lung but did not appear attached to the chest wall. It contained an area of radiolucency, 1.5 cm. in diameter, but a definite fluid level could not be demonstrated. A few flecks of calcification were present in the lesion. A coarse strand of increased density was present in the basal segment of the left lower lobe, and there was slight blunting of the left costophrenic sinus posteriorly. The

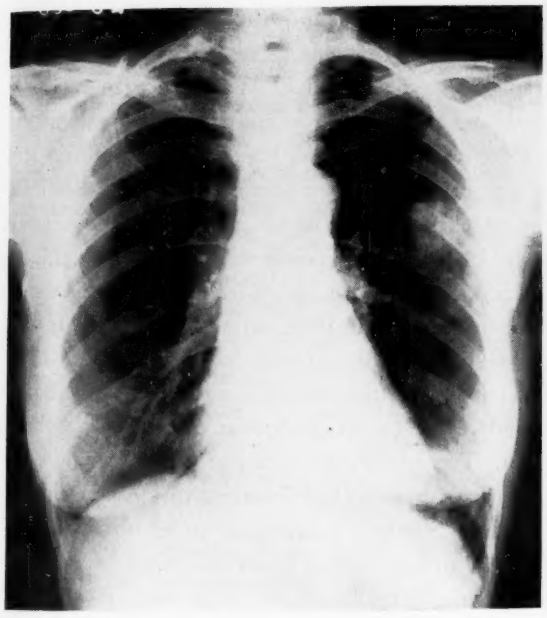

FIGURE 1.

remaining lung fields were clear. The heart was enlarged, and the aorta slightly sclerotic.

Two whole-blood transfusions of 500 cc. each succeeded in elevating the hemoglobin from 11 to 15 gm. but the leukopenia was unaffected. The erythrocytes were described as generally normocytic and slightly hypochromic, with slight anisocytosis and poikilocytosis. The platelets were abundant, and no abnormal leukocytes were seen. A sternal aspiration showed diffuse bone-marrow hypoplasia. No clinical changes were noted in the patient's condition.

An operation was performed on the ninth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. LOWREY F. DAVENPORT*: Since there are no definitive data and the differential diagnosis is going to depend largely on the interpretation of the x-ray films, I should like to see them at this point.

DR. STANLEY M. WYMAN: The two sets of films were taken approximately two weeks apart. In both there is seen a quite sharply defined rounded homogeneous shadow (Fig. 1 and 2), which lies midway in the chest in the anteroposterior diameter, possibly in the left upper lobe. There is a faint radiolucency within this dense shadow seen on both examinations that appears somewhat lobu-

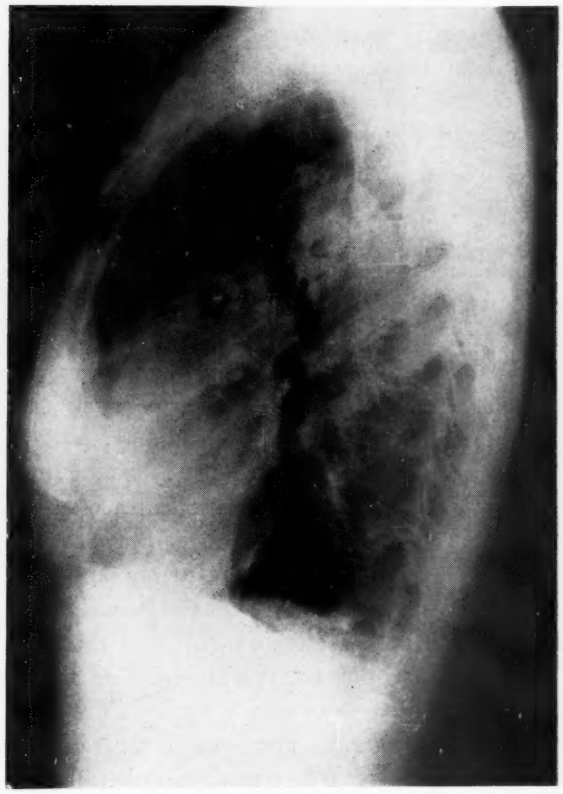

FIGURE 2.

lated but not shaggy or irregular. In addition this patient has calcific and fibrotic scars in the right first and second interspaces, suggesting old tuberculosis. There is some calcification in the hilus to go along with this. There is mottled linear increased density in the left lower lobe and probably to a lesser degree in the right lower lobe that suggests an old chronic process of some sort. The major bronchi are not remarkable.

DR. DAVENPORT: I am faced with the diagnostic differential of a discrete, nodose type of lesion located in the left-upper-lung field of a woman sixty-four years of age. The recent chest survey has turned up many discrete, nodose types of lesions. In many of these cases it has been much more difficult to decide to explore than in this case. Under obser-

*Assistant in medicine, Massachusetts General Hospital.

vation this tumor increased in size, and showed central excavation and beginning cavitation. The necessity for exploration was quite clear. In most of these cases, with this "coin" type of shadow and when the capsule is intact, it is useless to try to pursue lengthy differential diagnostic studies. If the capsule is intact in a tuberculoma, it is quite obvious that repeated examinations of the sputum will be of no help in making a diagnosis of tuberculosis. In the cancerous, nodose lesion, if the capsule is intact and the tumor is not exfoliating, it is impossible to pick up any cytologic data from bronchoscopic washings or examination of the sputum even with the Papanicolaou technic. This type of tumor is frequently beyond the range of the bronchoscope. We are forced in many of these cases to say: "Whatever the lesion, benign or malignant, tumor or infection, it had best be explored."

In the particular case the differential diagnosis, of course, is between infection and tumor and, if tumor, whether benign or malignant. On a percentage basis a good differential point has been age and sex. However, the incidence of bronchogenic cancer has increased appallingly, and the median age at which it is found is becoming lower. Within the past month, we have had a man with a bronchogenic cancer at the age of twenty-nine who I believe is the youngest to my knowledge that we have had come through the Bronchoscopic Clinic within the past ten years.[1] Was this infection, — a tuberculoma that was beginning to show central cavitation — or was it cancer? The differential diagnosis should also include the rather remote possibility of a metastatic nodule. The fact that this tumor had been observed over a period of three years would rule out with reasonable certainty the possibility of a metastatic nodule. The only exception to this generalization is the occasional case of hypernephroma with a solitary nodose type of metastatic nodule.

The presence of calcification in the periphery of the shadow here is of some differential importance but is not definite enough for us to be certain of the nature of the lesion. In general, calcification suggests a diagnosis of a tuberculoma rather than tumor. However, calcification is seen in metastatic tumors. For example, lymphosarcoma metastasizing to the lung can show a definite, round, discrete nodule with calcification in the center. The benign types of tumors, the adenomas and teratomas, occasionally show definite discrete calcifications on x-ray examination.

The history does not suggest benign adenoma. There are several points against it. Most of the adenomas encroach upon the lumen of the bronchus early, and the clinical story is that of repeated episodes of partial or complete bronchial obstruction. There was no evidence in this history or in the x-ray findings that there was involvement of the bronchial wall itself, and I shall therefore exclude the benign tumors — the adenomas, the teratomas and the dermoids — from the differential diagnosis.

An intriguing temptation here is to try to link up the leukopenia and the relative depression of the polymorphonuclear leukocytes with the tumor seen in the x-ray films. We have seen on several occasions Hodgkin's lymphoma with parenchymal nodose lesions that have gone on to cavity formation. In several such cases the rounded, discrete lesions in the parenchyma of the lung with abscess formation have been clearly connected with enlarged hilar lymph nodes. I will therefore exclude lymphoma in spite of the temptation to try to bring the blood picture into the diagnosis.

I think the differential diagnosis should be narrowed down to bronchogenic cancer or a tuberculoma. The peripheral types of bronchogenic cancer in general are most likely to be the adenocarcinomas. The fact that this tumor was under observation for a period of some three years is against bronchogenic carcinoma, but I cannot quite exclude it. Many of us will recall the case[2] discussed here several years ago that turned out to be a well differentiated epidermoid cancer even though the lesion had been seen on x-ray examination for more than eight years. A three-year history of x-ray evidence of a tumor does not, then, exclude the possibility of a malignant process.

The age of this patient is somewhat against a diagnosis of tuberculosis, but either a nodose tuberculosis with central cavitation or a bronchogenic cancer with beginning necrosis could give an x-ray shadow such as we see here and the symptomatology as described in the protocol. I see no way of making a differential diagnosis between these two possibilities except on a percentage basis. Because of the fact that the mass had been present for three years and that there was surrounding calcification with central necrosis, I would make my first diag-

nosis a solitary tuberculous lesion, a so-called tuberculoma, with beginning necrosis, and my second diagnosis a bronchogenic cancer, with beginning central necrosis and cavity formation.

It seems to me in these cases that Dr. Allen O. Whipple's[3] remarks concerning cases of jaundice are equally applicable, "if only these patients could be referred . . . before they are studied to death. . . ." Valuable time can be lost in pursuing a differential diagnosis where surgical resection is clearly indicated from the beginning. However, there is certainly a midground between clinics that report positive bronchoscopic biopsy after six attempts and other clinics where resection of a tuberculoma has been done through an active bronchial tuberculous lesion not determined by previous study. In this case I would be committed to taking out the left upper lobe whether or not there was bronchogenic carcinoma or tuberculosis.

Dr. Bernard M. Jacobson: I saw this patient at Dr. Churchill's request. The moderate leukopenia could not be explained by any specific diagnosis. The postoperative course was characterized by nothing unusual clinically. The white-cell count, with the postoperative fever, rose to 11,000 or 12,000 with a fairly normal differential, and the leukopenia was nearly gone by the time the patient left the hospital.

Dr. Walter Bauer: I think there is one thing that might be said regarding a nodular lesion of this type whether cavitation is present or not — not that what I have to say applies to the case under discussion. If one were confronted by a case of this type in the southwestern part of this country, one certainly would have to entertain very seriously the possibility of a coccidiomycosis granuloma. The original description of the cavitation seen in coccidiomycosis emphasized that the cavities had paper-thin walls; however, it has subsequently been shown that sloughing of the central portion of the granuloma results in a nodular lesion, with cavitation not unlike that seen in a tuberculous granuloma.

Clinical Diagnosis

?Carcinoma of lung.
?Pulmonary tuberculosis.

Dr. Davenport's Diagnosis

Tuberculoma of lung; ?bronchogenic carcinoma.

Anatomical Diagnosis

Tuberculoma of lung.

Pathological Discussion

Dr. Austin L. Vickery: The operation referred to in the protocol was that of a biopsy of a lymph node in the right axilla, and this proved to be an enlarged lymph node almost entirely replaced by a tuberculous lymphadenitis, largely caseous. A few days later a left upper lobectomy was performed, and in the lateral aspect of the posterior apical segment was an area of scarring of the pleura under which a rubbery node could be felt. This on section proved to be a pretty well circumscribed laminated mass with a central area of cavitation about 1.5 cm. in diameter that corresponded to the area of translucency Dr. Wyman pointed out. Microscopically, this was a typical tuberculoma. There was no demonstrable communication of the adjacent bronchi with this mass. However, in the immediate vicinity there was some atelectasis of the lung tissue, and a small bronchus showed some active tuberculous inflammation. In addition, there were five hilar lymph nodes, all of which showed the same disease.

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COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

AMERICAN COLLEGE OF SURGEONS

BOSTON, having played host in recent years to a number of important national medical organizations, including the American Public Health Association and the American College of Physicians, may now look forward to the additional privilege of entertaining this fall the American College of Surgeons.

The eminent sawbones that make up the fellowship of the College, now over 15,000 strong, will enable the historic city to bask once more in the strong light of a reflected glory. This, the thirty-sixth clinical congress, is expected to fill to overflowing Boston's hoary Mechanics Building and make its ancient rafters ring.

During the Congress, from October 23 to 27, operative clinics will be held at twenty-four hospitals of the metropolitan district, and the twenty-ninth annual hospital standardization conference will take a prominent place among the various official meetings, scientific sessions, motion pictures and technical exhibits. Five thousand or more surgeons are expected to attend the gathering, with hotel headquarters at the Statler and Copley Plaza.

Dr. Arthur W. Allen, of Boston, former president of the College, is chairman of the Board of Regents, and Dr. Frederick A. Coller, of Ann Arbor, is president. Dr. Thomas H. Lanman is chairman of the Boston Committee on Arrangements. At the Presidential Meeting on Monday evening, October 23, Dr. Henry W. Cave, of New York, will be installed as president with Dr. Warren H. Cole, of Chicago, and Dr. G. Gavin Miller, of Montreal, as first and second vice-presidents.

The annual convocation will be held on the evening of October 27, at which time several hundred new fellows will be inducted into the College, the Fellowship Address being given by the director, Dr. Paul R. Hawley, on the subject "Quo Vadimus?"

The *Journal* takes pleasure in adding its welcome to those that are being extended to the College by many other institutions and organizations.

VETERANS DEFERRED?

WORLD WAR II veterans who are reserve medical, dental and veterinary officers should breathe more easily so long as instructions issued from the Office of the Surgeon General on September 12 remain effective. These instructions, the first fruit of the legislation providing for selective induction of physicians and other personnel, are expected to reduce from 50 to 75 per cent the number of these veterans to be recalled.

While the new policy will have no effect on total Army Medical Service recall requirements, according to Major General R. W. Bliss, Army Surgeon General, it will strengthen the preferred status of professional officers with World War II service. This policy is considered as an interim measure, "designed both to protect those with the most military service and assure an adequate number of professional officers for the Army before the new legislation becomes effective." It is expected that

three or four months will elapse between the passage of the legislation and the actual entering into service of the personnel involved.

The quota that each Army area commander is required to produce will remain as previously stated, but will now consist of two parts — the new special quota and the remainder of the over-all allocation. The special quota will be filled so far as possible with volunteers and reserve officers with no World War II service. Officers with World War II service will be recalled only when others are not available in the required grades and specialties. The remainder of the over-all quota must be filled with volunteer and reserve officers without wartime service, and will *not* be filled with World War II officers.

All officers with World War II service not included in recalls for the special quota in each Army area, the release concludes, will be temporarily deferred from recall, except those assigned to duty with organized units.

Such an order is obviously subject to change without notice, as the occasion demands, and it is suggested that members of the Officers Reserve Corps find out their status and apply for reserve commissions as advised by Dr. Goethals in his letter published in these columns two weeks ago.

FUNGOUS INFECTIONS OF THE SKIN

COMPARATIVELY few investigations of fungous infections of the skin in the Boston area have been made. However, the report by Downing, Baird and Paci, in this issue of the *Journal*, serves to emphasize certain features of such infections. In the first place, such a diagnosis, in accordance with good medical practice, should be supported by laboratory evidence. Microscopical examination of material — scales, hair, nail scrapings and tops of vesicles — removed from a lesion is a comparatively simple procedure, and culture studies of such material frequently give clues to therapy and prognosis. Secondly, the diagnosis of fungous infections of the feet and especially of the hands is all too readily made, for patients with such a diagnosis are frequently found, with further study, to have contact dermatitis, perhaps with a low-grade secondary infection. Thirdly, so many patients suspected of having a fungous infection of the skin are treated with strong antiparasitic agents, with subsequent development of a severe therapeutic dermatitis and perhaps considerable disability, that every precaution should be taken to prevent such a complication of a condition that, with proper treatment, would have been a mild dermatitis. Fourthly, it is brought out that most cases are of human rather than animal origin. Finally, it is fortunate that the Boston area has been spared the ringworm epidemics that have swept a number of the larger metropolitan areas of the country.

"Athlete's foot," "jungle rot" and "dhobie itch" are frequently used by the laity to characterize a fungous infection of the skin, but the terms are very loosely used and the physician should examine all the evidence in a given case, both clinical and laboratory, to make the most accurate diagnosis possible and thus to arrive at the best therapy for the individual patient.

HEGIRA CONTINUES

TRIBUTE has been paid in recent issues of the *Journal* to certain intrepid pioneers who, trained in New England and suckled, as it were, at the very bosom of Bostonian conservatism, have made their way into the west to accept positions of academic trust and distinction.

And now another name can be added to the list; that of Fiorindo A. Simeone, who has migrated to Cleveland from the Massachusetts General Hospital, where he has been assistant surgeon and assistant professor of surgery in the Harvard Medical School. In Cleveland Dr. Simeone has assumed the posts of professor of surgery at Western Reserve University School of Medicine and director of surgery at Cleveland City Hospital.

Westward (again) the course of empire takes its way!

The New York Express has a leader on Mr. Littlefield, late janitor of the Medical College where Dr. Parkman was murdered; and Mr. L. receives a severe castigation for travelling with a model of the College and wax figures of Parkman and Webster. Mr. L. has since discontinued his very objectionable course.

Boston M. & S. J., *October 9, 1850*

BOSTON MEDICAL LIBRARY

ANNIVERSARY DINNER

The Massachusetts Medical Society members and their guests are cordially invited to attend the seventy-fifth anniversary dinner of the Library to be held at the Hotel Kenmore, Boston, at 6:30 on the evening of October 18.

Dress will be optional.

Applications for tickets at $4.50 each should be received at the Library at 8 Fenway not later than October 16.

The Library will be closed to the public on October 18, and the usual services to members discontinued. "Open House" will be held from 9 to 5 for all members and their friends.

EXHIBIT

An exhibit of books and other material concerning the development of medicine in Boston and its vicinity, arranged by the director of the Library, will be held at the Boston Public Library from October 18 to December 18. The exhibit is open to the public.

CORRESPONDENCE

HORRORS OF WAR

To the Editor: I read with a great deal of interest the article by Dr. U. K. Kiviranta entitled "Liquor Adulterated with Lye as a Cause of Dysphagia and Stricture of the Esophagus" in the August 10 issue of the *Journal*.

During my service as chief of the Gastrointestinal Section at Walter Reed General Hospital, Washington, D. C., during World War II, we encountered a group of patients with esophageal stricture somewhat similar to that described in Dr. Kiviranta's report. In our cases, we were dealing with soldiers who had received their strictures in an interesting but curious way during the Battle for Germany.

With typical Nazi cunning, the German troops had observed that whenever our soldiers captured a town, the first places that they visited were the liquor stores and wine cellars to commandeer such supplies as were left, usually for their own use. In a number of cases there were calamitous results. When the captured liquor was drunk symptoms of burning of the mouth and about the lips were encountered. This necessitated medical attention, and in a considerable group of patients strictures of the esophagus, as related by Dr. Kiviranta, developed. On examination of the liquor involved, it was found that the Nazis had, with malice aforethought, adulterated the liquor, usually with lye or some other corrosive substance.

The American enlisted men, in their inimitable phrase-making fashion, soon applied the term "booby-trap cognac" to the adulterated liquor. At Walter Reed General Hospital it was common to call the esophageal strictures, requiring many months of dilatation, the "syndrome of booby-trap cognac."

IRVING B. BRICK, M.D.

Washington, D. C.

NOTICES

BOSTON CITY HOSPITAL HOUSE OFFICERS' ASSOCIATION

The Boston City Hospital House Officers' Association will present the following lectures, to be given in the new Cheever Amphitheater of the Dowling Building at 7 p.m., in its evening lecture series:

October 17. Roentgen Aspects of Three Rare Diseases: Hemachromatosis, vitamin D intoxication and renal calcinosis. Merrill C. Sosman, M.D., radiologist, Peter Bent Brigham Hospital.

October 20. The Present Status of Phlebothrombosis, Thrombophlebitis and Thromboembolism. Alton Ochsner, M.D., professor of surgery, Tulane University of Louisiana School of Medicine.

October 24. An Office Cardiac Examination. Samuel A. Levine, M.D., clinical professor of medicine, Harvard Medical School.

October 31. Vasovagal Mechanisms. The action of adrenalin and noradrenalin on the peripheral circulation of man. Henry Barcroft, M.D., Sherrington School of Physiology, St. Thomas' Hospital, London, England.

All interested persons are invited to attend.

WOMAN'S AUXILIARY TO MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

A luncheon and "Fashion and Furs" show (sponsored by Lamson and Hubbard) will be held at The Meadows, Framingham, on Tuesday, October 24, at 12:30 p.m. The cost of the luncheon is $2.50.

All Auxiliary members and their friends are invited. Those wishing to attend should send notification, specifying number of guests, together with a check, to Mrs. G. G. Bailey, 153 Washington Street, Belmont.

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, November 1. The scientific session, conducted by Dr. Allan M. Butler and members of his staff, will be held in the amphitheater of Building C, Harvard Medical School, from 2:30 to 5:00 p.m. At the evening session at Longwood Towers, Brookline, Dr. V. Everett Kinsey, assistant professor of ophthalmic research at Harvard Medical School, will speak on the subject "Present Status of Retrolental Fibroplasia."

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The annual convention of the Association of Military Surgeons of the United States will be held at the Hotel Statler, New York City, on November 9, 10 and 11. The programs will deal with civil defense, the defense role of the physician, aviation medicine, rehabilitation medicine, military medicine, surgery and sanitation, with discussions on the use of the newest therapeutic and prophylactic agents in emergency conditions. Section meetings for dental, nursing, veterinary and other specialty groups will be included, and several of the sessions will deal with the problems of the medical reserve.

NEW YORK STATE SOCIETY OF ANESTHESIOLOGISTS

The fourth annual Postgraduate Assembly of the New York State Society of Anesthesiologists will be held at the Hotel New Yorker, New York City, on December 7, 8 and 9. There will be nine scientific sessions devoted to fundamental and recent subjects of concern to surgeons and anesthesiologists. Each session, in panel format, will be conducted by an accepted authority on the subject to be discussed. One panel will be presented by residents and fellows in anesthesiology discussing original investigations in which they have participated.

Physicians desiring to attend the meeting may obtain a registration form from the office of the Society at 137 West 11 Street, New York City.

(*Notices concluded on page xvii*)

NOTICES (*Concluded from page 582*)

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 13. Chemotherapy — New Preparations, Their Efficacy and Effects. Dr. Chester S. Keefer. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

OCTOBER 14–19. American Academy of Pediatrics. Page 962, issue of June 15.

OCTOBER 17. South End Medical Club. Page 512, issue of September 28.

OCTOBER 17. Boston City Hospital House Officers' Association. Page 582.

OCTOBER 20. Boston City Hospital House Officers' Association. Page 582.

OCTOBER 23–27. American College of Surgeons. Page xi, issue of June 29.

OCTOBER 23–28. Medicomilitary Symposium for Officers of Fourth Naval District. Page 34, issue of July 6.

OCTOBER 24. Woman's Auxiliary to Middlesex South District Medical Society. Page 582.

OCTOBER 24. Boston City Hospital House Officers' Association. Page 582.

OCTOBER 28. Massachusetts Association of Medical Technologists. Page 324, issue of August 24.

OCTOBER 30–NOVEMBER 3. American Public Health Association. Page 240, issue of August 10.

OCTOBER 31. Boston City Hospital House Officers' Association. Page 582.

OCTOBER 31–NOVEMBER 3. International College of Surgeons. Page 170, issue of July 27.

NOVEMBER 1. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 1. Hampshire District Medical Society. Page 170, issue of July 27.

NOVEMBER 1. New England Pediatric Society. Page 582.

NOVEMBER 5 AND 6. American Society for the Study of Arteriosclerosis. Page 170, issue of July 27.

NOVEMBER 6–8. New England Postgraduate Assembly. Hotel Statler, Boston.

NOVEMBER 6–9. International Medical Assembly. Page 548, issue of October 5.

NOVEMBER 9–11. Association of Military Surgeons of the United States. Page 582.

NOVEMBER 10. American Trudeau Society. Page 280, issue of August 17.

NOVEMBER 14. New England Society of Anesthesiologists. Page 512, issue of September 28.

DECEMBER 7–9. New York State Society of Anesthesiologists. Page 582.

JANUARY 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

FEBRUARY 13. New England Society of Anesthesiologists. Page 512, issue of September 28.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

NOVEMBER 1. 4:30 p.m. Northampton State Hospital.
JANUARY 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
MARCH 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
MAY 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

MIDDLESEX SOUTH

OCTOBER 24. Woman's Auxiliary. 12:30 p.m. The Meadows, Framingham.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 19

FRIDAY, OCTOBER 20

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.
*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.
*7:00 p.m. Boston City Hospital House Officers' Association. Dowling Building.

MONDAY, OCTOBER 23

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, OCTOBER 24

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
12:30 p.m. Woman's Auxiliary to Middlesex South District Medical Society. The Meadows, Framingham.
*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*7:00 p.m. Boston City Hospital House Officers' Association. Dowling Building.

WEDNESDAY, OCTOBER 25

*12:00 m. Clinical Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.
*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

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For further information apply to the DEAN, BOSTON UNIVERSITY SCHOOL OF MEDICINE, 80 East Concord Street, Boston, Massachusetts.

*There will be no exercise on November 8 because of the New England Postgraduate Assembly.

Index to Advertisers

	PAGE
Adams House	xvi
American Policyholders' Insurance Co.	iv
Ar-Ex Cosmetics, Inc.	xii
Aspinwall Nursing Home	xii
Ayerst, McKenna and Harrison, Ltd.	ix
A–Z Research Laboratory	xii
Baldpate, Inc.	xvi
Boston Medical Supply Company	xii
Boston University School of Medicine	xvii
The Channing Home	xvi
The Coca-Cola Company	xiv
Crosbie–Macdonald	xiv
David Memorial Nursing Home	xvi
Davies, Rose and Company, Ltd.	vi
Glenside, Inc.	xvi
Institute for Speech Correction, Inc.	xvi
Kenmore Pharmacal Company	iv
Leary Laboratory	xii
Lederle Laboratories	v
Eli Lilly and Company	Front Cover
M & R Dietetic Laboratories, Inc.	viii
Mead Johnson and Company	Back Cover
Medical Clearing Bureau, Inc.	iv
Merck and Company, Inc.	xv
New England Postgraduate Assembly	xi
Perkins School	xvi
Charles Pfizer and Company, Inc.	xiii
Rexair Division, Martin–Parry Corp.	iv
R. J. Reynolds Tobacco Company	vii
Ring Sanatorium	xvi
Washingtonian Hospital	xvi
Westwood Lodge, Inc.	xvi
White Laboratories, Inc.	iii
Winthrop–Stearns, Inc.	x
Wiswall Sanatorium	xvi
Woodside Cottages, Inc.	xvi

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